The Journal of Bone and Joint Surgery

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The American Orthopaedic Association
The British Orthopaedic Association
The American Academy of Orthopaedic Surgeons
The Australian Orthopaedic Association
The Canadian Orthopaedic Association
American Society for Surgery of the Hand
New Zealand Orthopaedic Association
South African Orthopaedic Association

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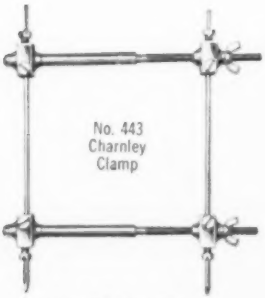

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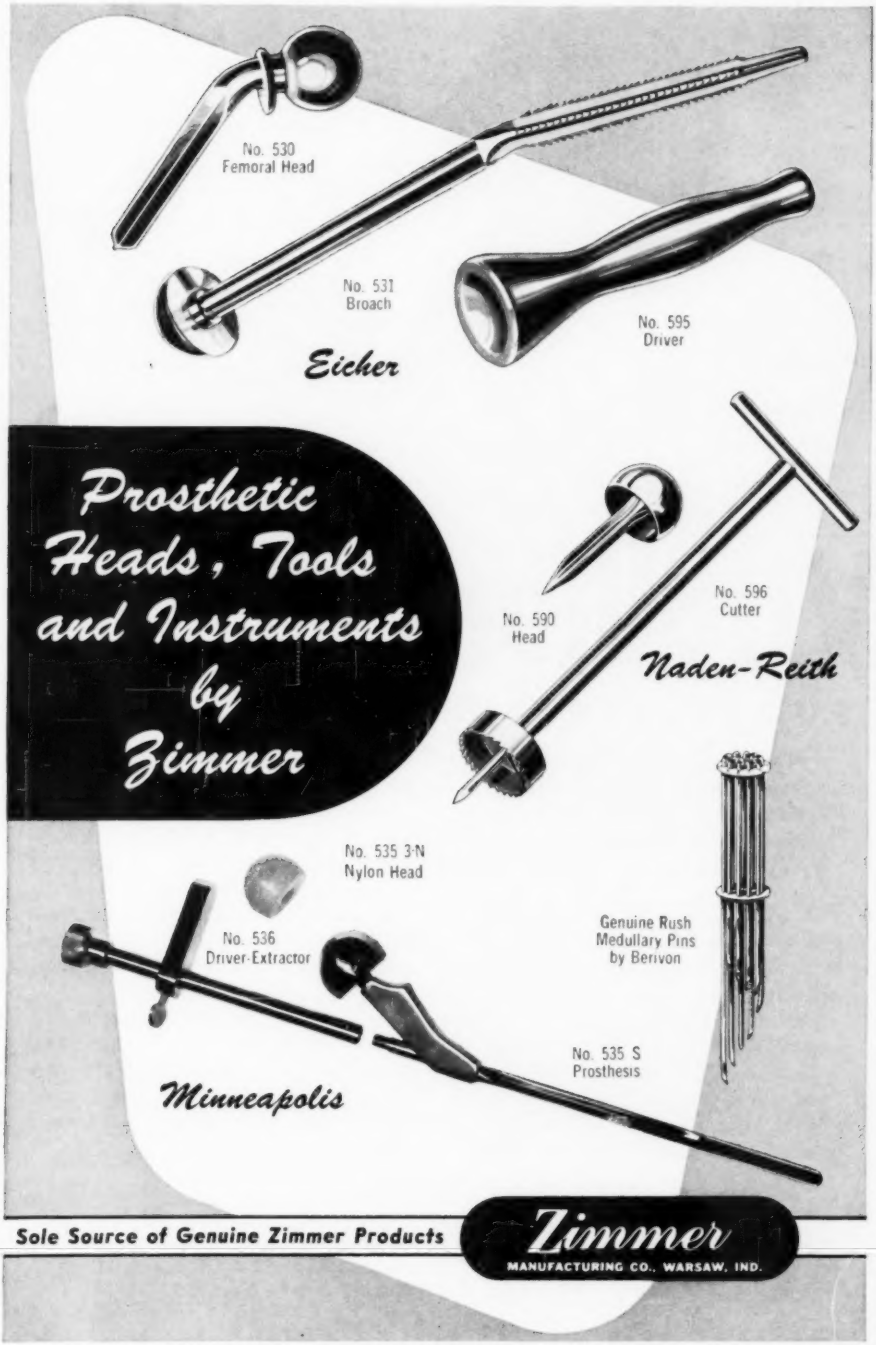
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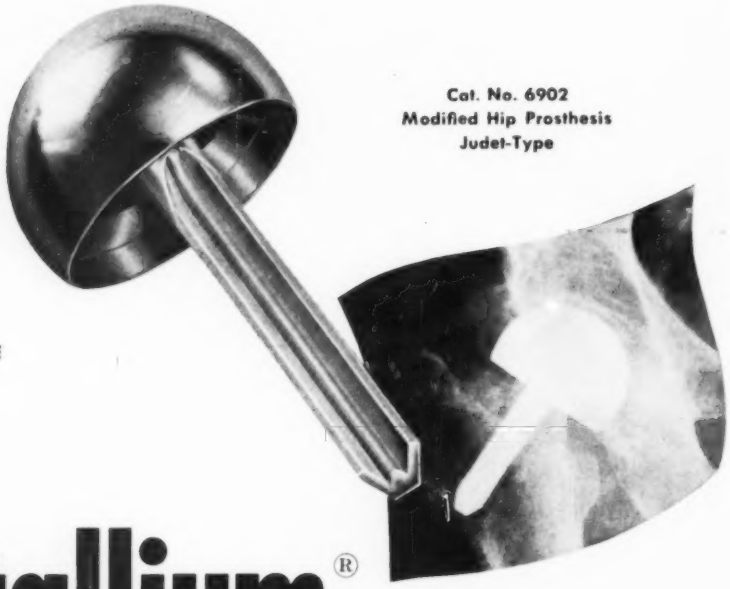

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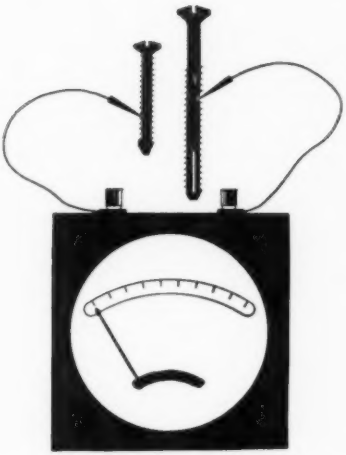

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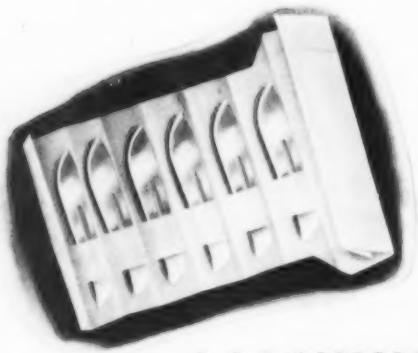

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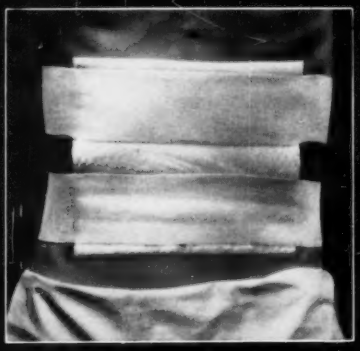

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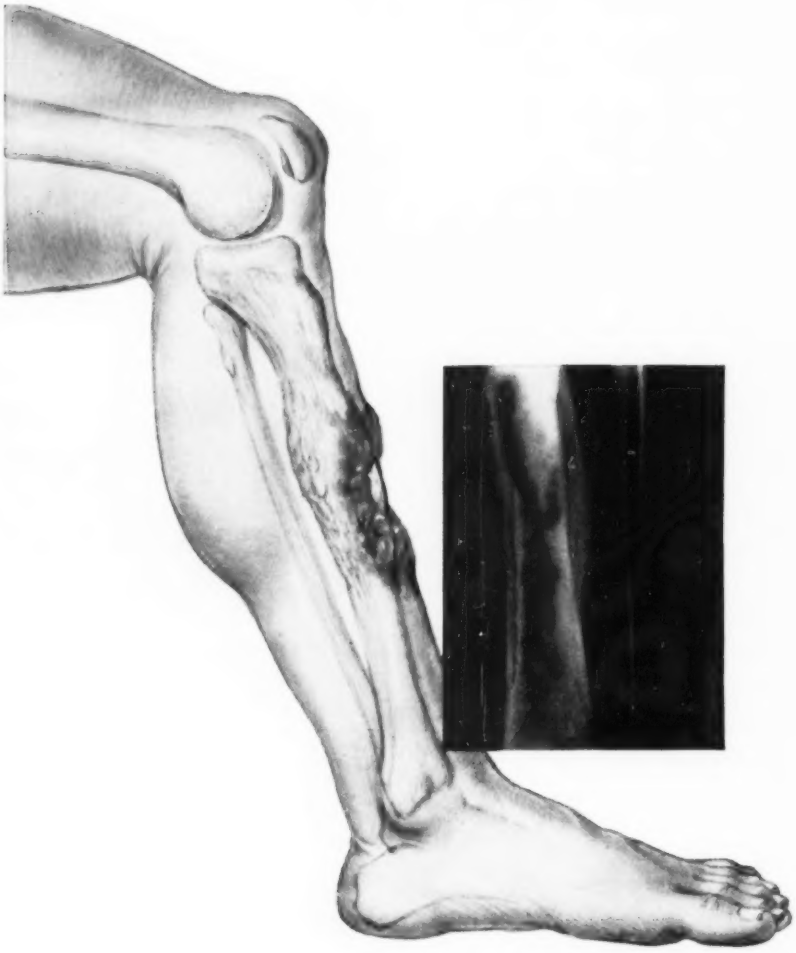

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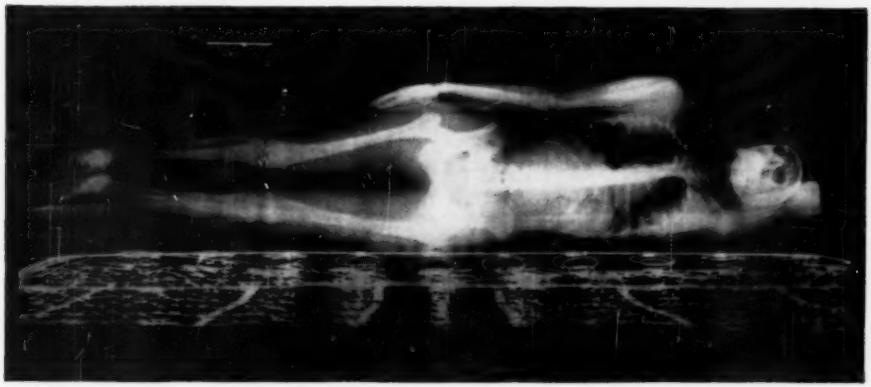

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After more than two years of research, study and investigation by a group of scientific workers, and the construction of complicated and costly roentgen apparatus and the development and application of intricate radiographic technic, we present to you an X-ray answer to this speculation. The film shows a living, human, female figure on an Englander Mattress of Goodyear's Airfoam* and Englander's Red-Line★ Foundation.

As interpreted to us, it indicates that with this combination of mattress and foundation, a person can lie comfortably and without distortion of the head, neck, shoulders, torso, pelvis and extremities; that he can be comfortable without tension or distortion.

Actual reproductions of this roentgenogram on acetate film and a description of the research project and its findings have been prepared. We will be glad to send you copies of this material, without obligation, so that you can make your own interpretation and analysis of this interesting new research into healthful sleep. Just mail the coupon below or drop us a post card.

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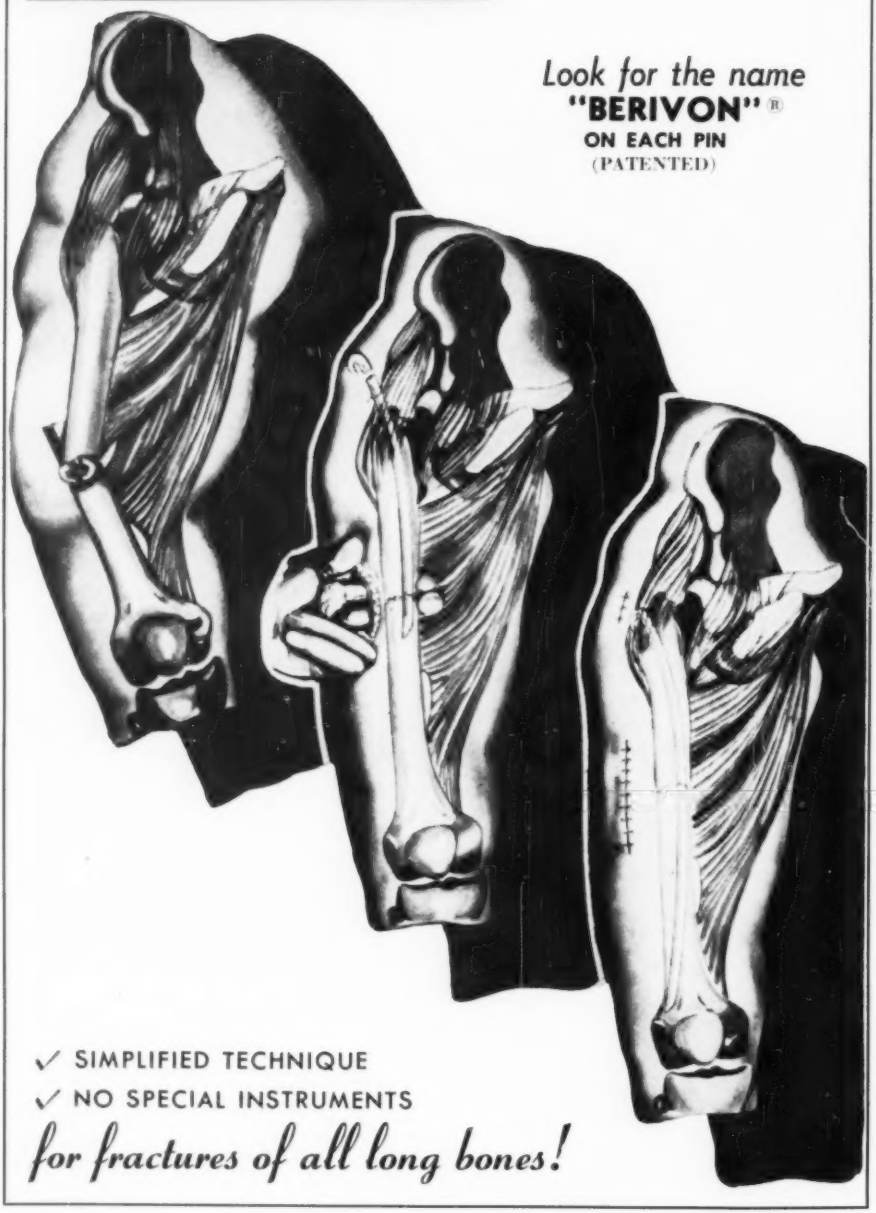
Please send me, free, actual reproduction on acetate film of roentgenogram showing living person on mattress and foundation and the description and findings.

Dr. _____

Address _____

City _____

The RUSH MEDULLARY PIN



Look for the name
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ON EACH PIN
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✓ SIMPLIFIED TECHNIQUE
✓ NO SPECIAL INSTRUMENTS
for fractures of all long bones!

The RUSH MEDULLARY PIN

- ✓ FOR ALL LONG BONES
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- ✓ CASTS RARELY NEEDED . . .

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Optimum temper based on fifteen years' research

The Rush Intramedullary Pin is fashioned from Type 316 stainless steel which has been specially hardened to the temper which clinical research has shown to be optimum for this purpose.

The Pin is designed to not completely fill the medullary canal of the bone, and is constructed so that it can be introduced axially into the bone through either the end or side.

No special instruments are required. The Pin is introduced into the bone through a suitable drill hole and is driven in with the mallet. A sled-runner point simplifies the introduction of the Pin into the medullary canal. The smallness of the diameter of the Pin and its temper permits it to take a curve to facilitate its introduction while having sufficient resilience to realign itself within the bone. The security of the fixation utilizes the normal muscle pull of an extremity to secure three-point pressure within the medullary canal.

Techniques have been worked out making it possible to fix many fractures near joints which heretofore have not been accomplished by other forms of medullary fixation.

A special hooked head prevents the Pin from migrating into the bone. This head makes it possible to remove the Pin by the use of the screw driver and mallet. A pair of pliers is an excellent adjunct in both insertion and removal of the Pin as it can be guided by rotation.

NOTE: All authentic Rush Pins bear the trademark BERIVON. ®

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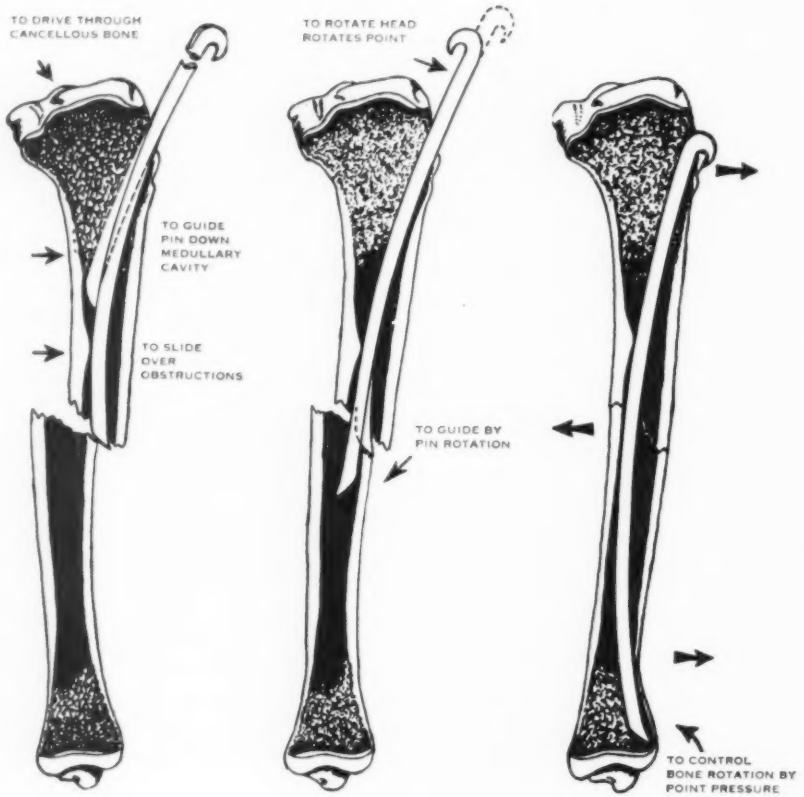
The RUSH MEDULLARY PIN

Why The Sled Runner Point


TO DRIVE THROUGH CANCELLOUS BONE
TO GUIDE PIN DOWN MEDULLARY CAVITY
TO SLIDE OVER OBSTRUCTIONS
TO ROTATE HEAD ROTATES POINT
TO GUIDE BY PIN ROTATION
TO CONTROL BONE ROTATION BY POINT PRESSURE

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The RUSH MEDULLARY PIN

For Dynamic Fracture Fixation

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if it isn't BERIVON
it isn't a Rush pin

Femur, Tibia

RACK ONE: ¼ inch diameter, lengths 11 to 17 inches, 9 pins to the rack.
Price by rack ..... $7.50 per pin

Humerus, Tibia, Femur

RACK TWO: 3/16 inch diameter lengths 8 to 14 inches, 9 pins to the rack.
Price by rack ..... $6.00 per pin

Radius, Ulna, ankle region, neck of humerus, humeral condyles, condyles of femur and tibia.

RACK THREE: ⅛ inch diameter, lengths 4 to 10 inches, 14 pins to the rack.
Price by rack ..... $4.00 per pin

Small bones, clavicle, jaw, metacarpals, humeral condyles, etc.

RACK FOUR: 3/32 inch diameter, lengths 1 to 4 inches, 13 pins to the rack.
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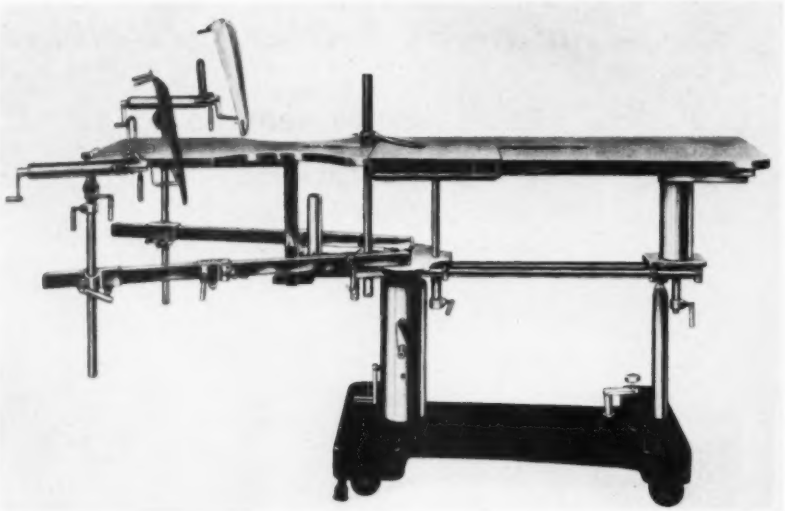

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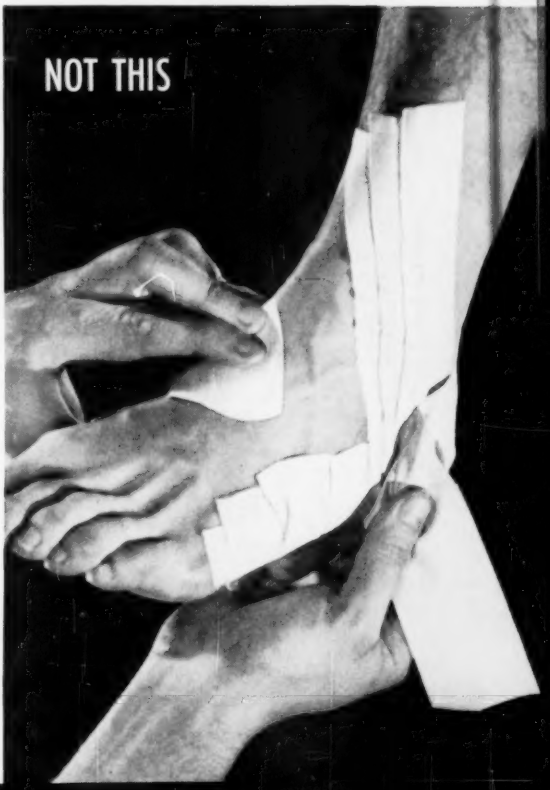

Smooth, fast, wrinkle-free taping is assured in *New* Curity adhesive by a special cloth backing which reduces wrinkling . . . yet is *flexible* to permit you to work fast with sure, smooth results.

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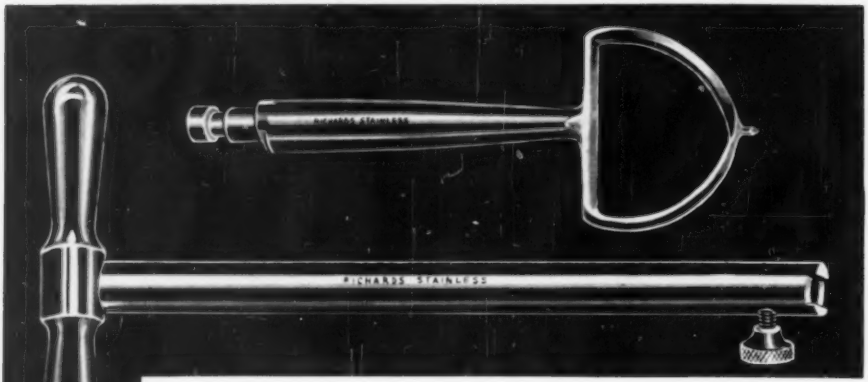

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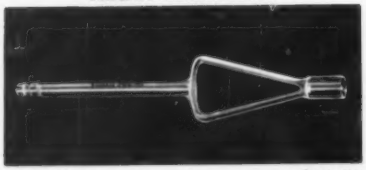

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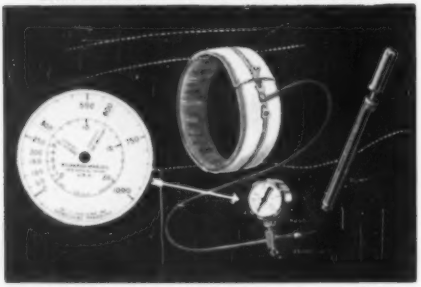

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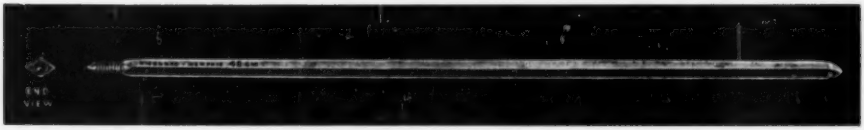
THE **NEW** HANSEN-STREET
INTRAMEDULLARY NAIL FOR THE FEMUR

SMO STAINLESS STEEL



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This nail, with the new pointed and threaded head, is just what has been desired for the **Simplest, Easiest** and **Fastest** insertion of intramedullary nails. Insertion by retrograde is now accomplished with no difficulty, in that you are using the nail as its own guide, coming thru the trochanter with no shattering effect, merely by using your regular mallet of bronze or aluminum. After it has come thru the trochanter, an incision is made and the **New Extractor-Driver** is screwed on the head of the nail. Using the handle as holder for support, the nail is then driven back into the distal fragment, after approximation. Rotation is not possible with this type of nail.

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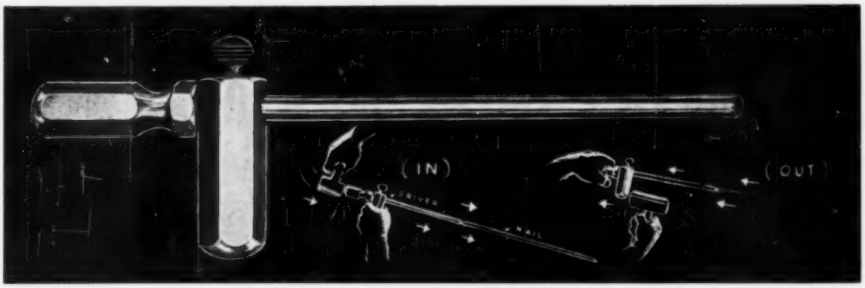
There is no need for further instruments to do a perfect, easy, and fast operation.



No. N-101 fits all nails	**$25.00**
No. 101S Short Driver 8″	**5.00**
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Acme Cruciate-Head Bone Screws are used and proclaimed by the majority of leading medical centers and by all branches of the United States Armed Forces. These screws have elevated the general concept and demanding requirements of bone screws to that of precise units of instrumental surgical mechanism, compatible in each minute detail of their manufacture to the vital function they perform.

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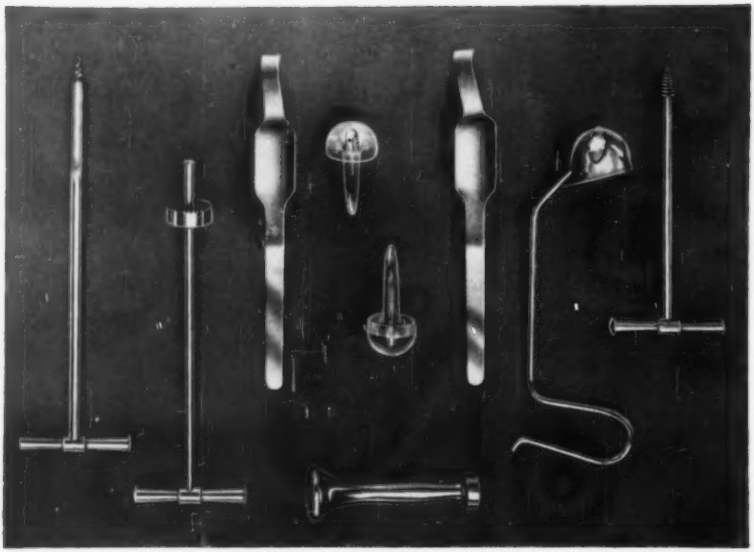

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Using a stemmed prosthesis in a simple method of femoral-head substitution, the Judet procedure has created widespread interest, both here and abroad. H. Kelikian, M.D., describes the technique in *The Armamentarium*, recently published. If you have not received your copy of this surgical bulletin, please write, and *The Armamentarium* will be sent to you promptly.

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Heads now also available with x-ray indicator and position control marker. *Each*, $40.00.

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Borer, with two diameters and depth guides. *Each*, $28.00.

Cutter, for trimming osteotomized neck to fit it exactly inside the contour of the Ossacryl head. *Each*, $30.00.

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which provides full traction, flexion, abduction and adduction facilities plus unobstructed radiographic approach

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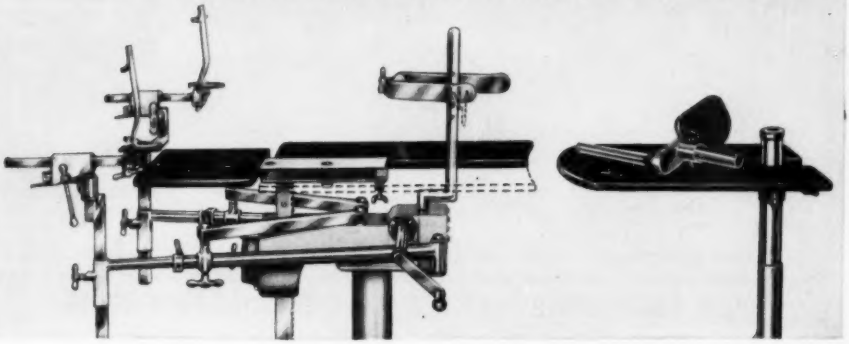

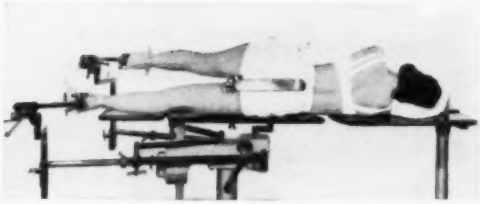

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Adducting offending extremity, the proximal fragment is exposed for driving the nail (or guide wire) retrograde.

These advantages will aid you clinically—

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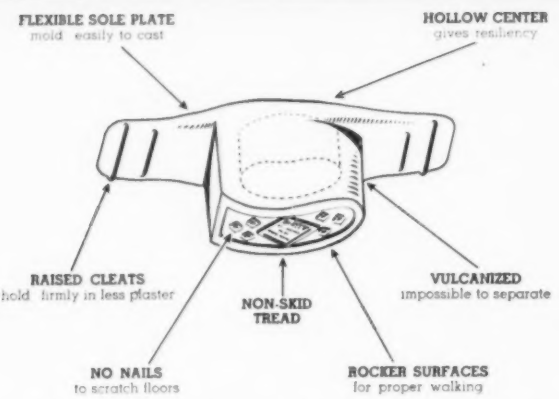

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Diameters: 11mm x 8mm, 9mm x 7mm

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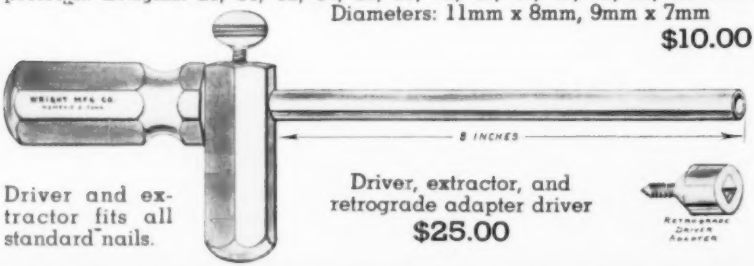

Driver and extractor fits all standard nails.

Driver, extractor, and retrograde adapter driver
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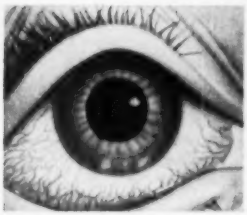
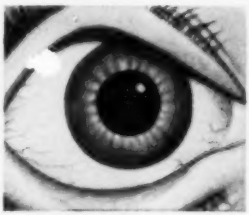


Pretreatment



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1. Scheie, H. G., Tyner, G. S., Buesseler, J. A., and Alfano, J. E., *J. A. M. A. Arch. Ophth.* 45:301, March 1951.

2. Leopold, I. H., Purnell, J. E., Cannon, E. J., Steinmetz, C. G., and McDonald, P. R., *Am. J. Ophth.* 34:361, March 1951.

Literature on request

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The bandage on the left is TENSOR—woven with live rubber threads

The photo tells the story. *Live rubber* threads in Tensor make the difference. Tensor doesn't depend merely on the weave of its fabric for elasticity.

Patients welcome greater mobility and comfort with Tensor. Firm, steady *support where it's needed*. Tensor stays put, retains proper pressure without frequent readjustment.

And Tensor *stays* elastic even after prolonged wear, stretching and laundering.

Isn't Tensor, then, your wisest possible investment in elastic bandages?

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ELASTIC BANDAGES

—woven with live rubber threads

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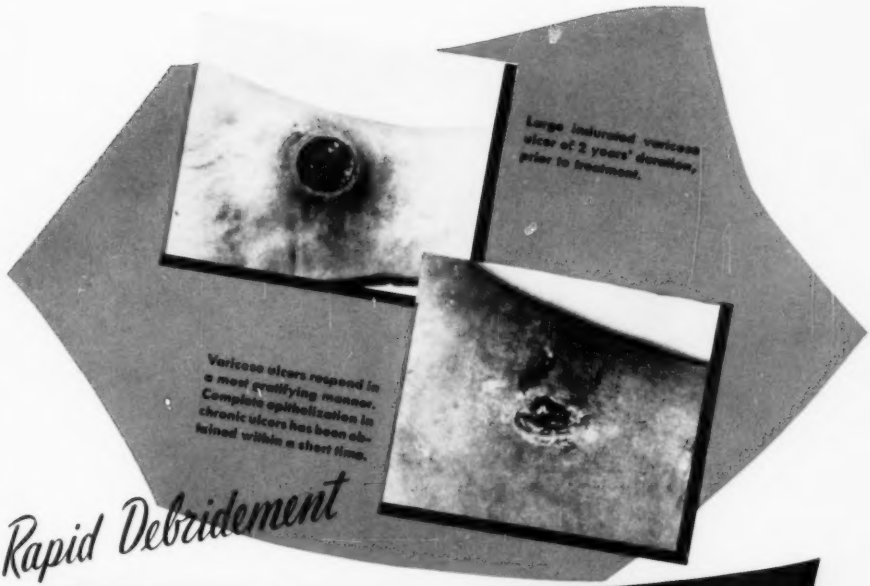
TENSOR depends on live rubber threads for greater elasticity.

CONVENTIONAL elastic bandage is all cotton, can't have Tensor's elasticity.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Varicose ulcers respond in a most gratifying manner. Complete epithelization in chronic ulcers has been obtained within a short time.

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IN INFECTED WOUNDS AND CHRONIC LESIONS

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SUPPLIED: Tryptar powder is supplied with Tryptar Diluent, and adapter for powder blower. Write for literature on methods of application.

In chronic lesions and infected wounds, Tryptar greatly facilitates healing by removing obstacles which interfere with the natural defense mechanisms of the body. Tryptar rapidly dissolves necrotic tissue, pus and pyogenic membranes by selective proteolytic digestion, without injury to living tissue. Control of topical infection is attained.

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Tryptar affords remarkable savings in medical care . . . dramatically reduces recovery time . . . shortens length of disability. Applied as powder or wet dressings.

1. Reiser, H. G., et al.: Arch. Surg. 63:568-575, 1951.

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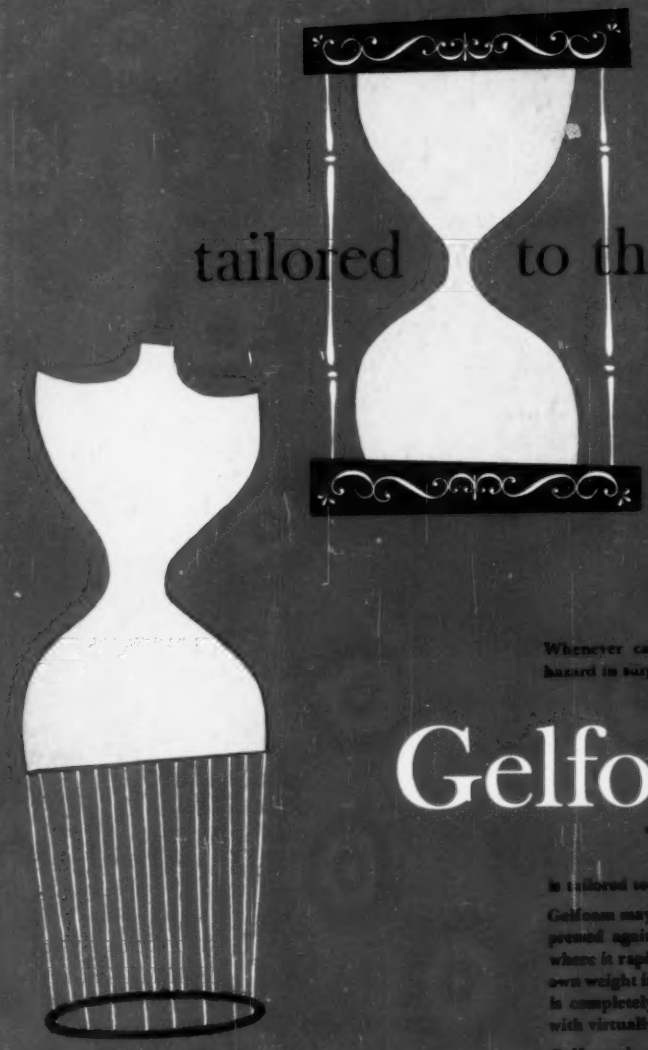

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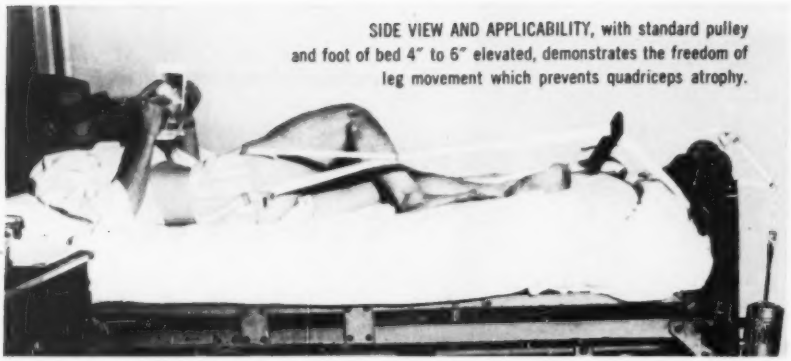

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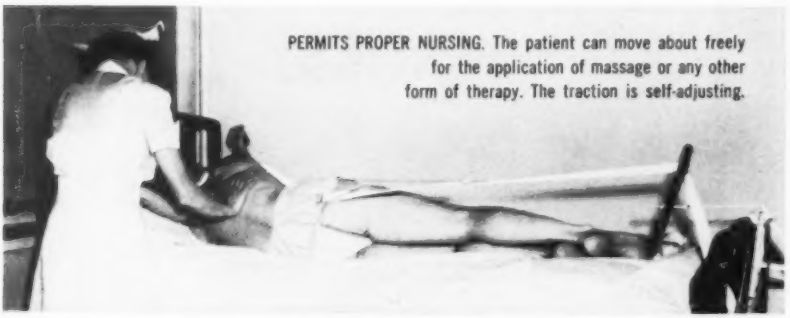

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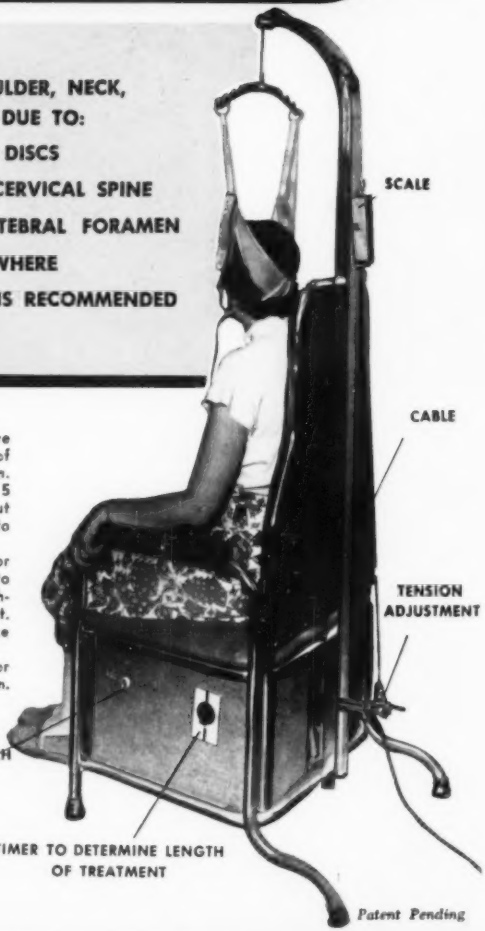

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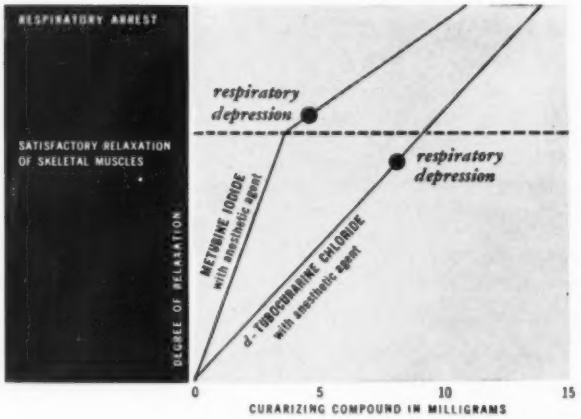

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VOL. 34-A, NO. 2 APRIL 1952

The Journal of
Bone and Joint Surgery

American Volume

THE SURGICAL EXPERIMENT *

BY JOSEPH S. BARR, M.D., BOSTON, MASSACHUSETTS

"Life is short and the art long, the occasion instant, experiment perilous, decision difficult." — *Hippocrates*

Life is the great experiment—never repeated under identical conditions. For the next few minutes you and I will be the subjects of a phase of this experiment—the Academy Presidential Address. True, such addresses have been given some eighteen times previously, but the conditions were not the same. There was a different speaker, a different audience, a different speech. The results of these experiments are difficult to determine; for who has the means to measure the impact of ideas on the human mind? New concepts, even if skillfully presented, may appear to make little impression on the listener. Deficient or congenitally malformed ideas scarcely live beyond the echo of the speaker's voice and die unwept, unhonored, and unsung. In spite of the danger of unhappy parenthood, speeches will be made, and presidents will take as long a view as the bifocals permit.

I would like to consider with you some aspects of the experiment which each surgeon undertakes when he operates upon a patient. We scarcely need to be reminded that every surgical operation *is* an experiment in which many variable factors are present, most of them not under the control of the surgeon. Because of these uncontrolled variables, the results of operative treatment are predictable only in a statistical fashion by *post hoc* analysis of results obtained in a significant number of similar cases. We recognize that the outcome in an individual case is not accurately predictable and that chance plays a role in determining the result.

The prospects for a good surgical result, however, are improved by eliminating or controlling unfavorable factors. For instance, we have learned that shock can be controlled or eliminated by good anaesthesia, control of hemorrhage, prompt replacement of blood loss, and gentleness in handling tissues. Wound infection is another variable factor, which can tip the scales toward a disastrous result. The ritual of aseptic technique and the beneficent effects of antibiotic drugs have lowered the chance of infection to an acceptable risk.

The variable factor which I particularly wish to consider today relates to the surgical materials left in the patient's body. Modern surgical techniques utilize and leave within the human body a great variety of materials and devices. Sutures of catgut, cotton, silk, wire, and nylon; fracture fixation materials, such as nails, pins, screws, and plates; devices, such as Vitallium cups for the hip; prosthetic replacements of nylon, acrylic, and various metals for the femoral head; tantalum plates for the repair of cranial defects; hemostatic agents, such as gelfoam and oxidized cellulose, are examples of the variety of materials in every-day surgical use.

Success or failure of the surgical procedure is determined in part by physical and biological properties of the materials used. Let me cite two examples of failure of surgical materials.

The first example illustrates the problem of physical failure. A surgeon whom I know

* Presidential Address presented at the Nineteenth Annual Meeting of The American Academy of Orthopaedic Surgeons, Chicago, Illinois, January 29, 1952.

was finishing an operation in which he had replaced the head of the femur with a beautiful, expensive prosthetic device. As he was closing the incision, his scrub nurse inadvertently dropped a spare duplicate of the device on the floor. It broke into several pieces. My surgeon friend was at once faced with questions of the utmost importance. Was the duplicate device defective, or are all of these particular devices inadequate in strength and will they break under slightly excessive physiological strain? For instance, if his patient should jump or fall two or three feet, would the device fail? The manufacturer, of course, is willing to replace the defective broken duplicate, but the surgeon is responsible for the selection of the device which was used. If it breaks, the manufacturer will disclaim responsibility. The luckless surgeon has an operative failure to add to his record and may face an embarrassing lawsuit. The patient experiences a calamitous misfortune.

There is very little information available on the incidence of operative failure due to defects in surgical materials. Surgeons and manufacturers are both understandably reticent on the subject. But I have no hesitancy in saying that I have had failures of surgical operations due to physical failure of the materials used, and I suspect that most of you could produce similar case reports.

Biological incompatibility of the material with the human body is another cause for operative failure, as illustrated by the second example. In this instance a knee arthroplasty was done, nylon film being used as a lining membrane. There was a severe local post-operative reaction, consisting in massive, phlegmonous thickening of the soft tissues, and synovitis of the knee with development of a draining sinus. On removal of the nylon film, the reaction promptly subsided; but the operative result is unsatisfactory. In this case the cause of failure may have been either an excessive foreign-body reaction or an allergic sensitivity of the patient to nylon. She volunteered the interesting information that she never wore nylon stockings because of skin sensitivity. This appears to be an example of failure due to biological incompatibility. It might easily have been mistaken for postoperative sepsis.

It is not my purpose to attempt a comprehensive classification of the types of failure of materials in surgical operations, but there are several which are of major importance:

Breakage, bending, *et cetera*, from excessive strain;

Material weakness due to corrosion;

Abscess formation or fibrosis due to excessive foreign-body reaction.

The surgeon's conscience, and in fact his common sense, tells him that the physical and biological properties of *every* type of material used within the human body can and should be adequately tested before it is released by manufacturers and distributors for general use. Scientific testing methods are available, which are much more accurate than clinical trial; and the human guinea-pig technique is to a large extent outmoded and indefensible. Yet there is an ever-increasing number of new devices, many of which have been inadequately designed and tested. Manufacturers of surgical materials and devices furnish little or no specification data and the surgeon, who has legal and moral responsibility to see that due care is exercised, has no means of substantiating the claims of the inventor and the manufacturer except the risky one of clinical trial.

Are we going to continue with this unhappy trial-and-error method of procedure or can we devise some better way of obtaining accurate scientific information which will allow us to select the best materials and to correctly design the devices which we need?

The following propositions appear to be fundamental to a sound approach to the problem:

1. All surgical materials used within the human body should be adequately tested by modern laboratory methods and the data concerning their physical and biological properties should be furnished to the surgeon, so that he may have sound information as a basis for appropriate selection of materials.

2. The design of surgical devices should be systematically analyzed, mechanically and biologically, to ensure that they adequately fulfill their function in the human body.

Testing of Materials

Modern engineering and testing laboratories have the equipment and the know-how to test and furnish specific data concerning the strength of surgical materials. The composition, internal structure, surface finish, and elastic properties of each material should be determined. Testing machines are available which can subject the materials to tension, shear, torsion, and compression strains. Endurance and impact tests can be designed to simulate conditions occurring in clinical use.

Corrosion of certain metals in living tissues has been studied by a number of investigators, but there has been no systematic comprehensive investigation of this subject. It is obviously unnecessary and undesirable to pursue clinical experiments in this field. *In vitro* corrosion tests should be carried out on all surgical materials, individually and in varying combinations, solutions similar in composition to body fluids being used. There is clinical evidence that metals such as Vitallium and stainless steel, which individually are inert, show a definite tendency to corrode if used together in the body. We should have accurate corrosion data on all surgical materials.

The biological reaction of living tissues to foreign bodies has been studied for a century or more, but quantitative determinations of the amount of the reaction have been attempted infrequently. Standard methods of measurement of foreign-body reaction should be devised and all surgical materials should be so tested.

Design of Materials and Devices

The form which a piece of surgical apparatus takes is often the chance result of a surgeon's suggestion and an instrument-maker's conception of how it should look. Too often, without further formality, the device is tried on a human guinea pig. If it fails structurally, it is modified and a new and better model is tried again.

Fortunately, there are methods more scientific than the trial-and-error technique for the solution of problems of design. A careful analysis of the function of the device is an essential first step. One must make an accurate estimate of the range and duration of the strain to which the apparatus will be subjected. In many situations, this information is not now available. This should be a fruitful field for future research efforts.

In the case of immobilizing devices—such as sutures, screws, and bone plates—one of the important considerations is the strength of the body tissues to which the device is attached. The forces transmitted to the device cannot exceed the tensile strength of structures.

Having determined the function of a device and estimated the forces to which it will be subjected in actual use, the designer can proceed to select appropriate materials, sketch a suitable form, size, and surface finish for the device, and work out a satisfactory method of fixation of the apparatus to the adjacent living tissues. A model of the device can then be made and tested in the laboratory to ensure that it has adequate strength with a predetermined factor of safety in excess of the strain to which it will be subjected in clinical use.

Resistance to corrosion and the biological reaction of the host tissues to the device can be predicted from tests made previously on the materials of which it is constructed. Devices so designed and tested are then ready for the ultimate experiment of clinical trial; we know that there are sound reasons to expect that the result will be successful and that certain variable factors which may lead to failure have been eliminated.

We may sum up by saying that there is need for better use of engineering and biological techniques in the selection of surgical materials and in the design of surgical devices for use within the human body. In present practice we fall far short of utilizing knowledge already available, and we are not expanding the frontiers of knowledge in this field as industriously as we should.

How can the present state of affairs be improved? How can we correlate and put to

work the scientific knowledge now scattered in many fields of endeavor—surgery, pathology, biology, metallurgy, engineering, materials testing, design and production, to name but a few.

Obviously surgeons and the medical schools with which they may be associated have inadequate resources for this tremendous task. The manufacturers and distributors of surgical supplies are equally helpless. Their answer is: "Tell us what you want, furnish blueprints and specifications, and we will make it, but it is not our job to tell the surgeon what he needs". Shall we turn to our government to enact legislation similar to the Federal Food and Drugs Act which would prohibit the use of certain materials and require standardization of devices to be used within the human body? Most of us would agree that Federal law is no solution to this problem. It might result in "confusion worse confounded".

I suggest that the medical profession join hands with the manufacturers and distributors of surgical equipment, to form a non-profit organization with the following powers:

1. To test surgical materials and devices and to issue certificates giving specified data concerning the mechanical and biological properties of the articles tested;

2. To conduct and encourage research and to disseminate knowledge in the broad field of surgical engineering;

3. To hold patents and to utilize income derived therefrom for the benefit of humanity;

4. To encourage such standardization of sizes and types of devices as may be in the best interests of the surgical patient;

5. To assist manufacturers in their efforts to produce better surgical materials at decreased cost.

There are organizations now in existence, such as the Chemical Foundation, Inc., and the Underwriters Laboratories, Inc., successfully operating along lines similar to those I am proposing.

In broad outline the form of this at present non-existent organization might be sketched in this fashion. It would be a non-profit corporation sponsored jointly by the medical profession and by the manufacturers of surgical supplies. Its board of directors would include leaders in the fields of engineering, biology, surgery, and manufacturing. The working staff and consultants would be chosen for their technical competence and would have complete engineering and biological laboratory facilities at their disposal. Perhaps we might call this organization the "National Surgical Laboratories, Inc.".

Upon appropriate request, the laboratory would test surgical materials and devices by suitable standard engineering and biological methods. Labels bearing a seal of approval and giving test data might be attached to materials and devices which pass the required tests.

Although the testing and certification of surgical materials and devices would be an important part of the organization's work, its activities would by no means be limited to that function. Its staff would systematically and constantly study the broad underlying problems in the field of surgical engineering. It would conduct, sponsor, and encourage research and would issue publications summarizing the results of its investigations.

It would be authorized to hold and administer patents and to utilize income derived therefrom for the furtherance of its work and for the benefit of humanity. I mention this with some premonition of trouble. The code of ethics of the medical profession forbids its members to hold patents for the benefit of an individual. On the other hand, competent authorities point out that the profit motive and an equitable patent law are powerful incentives to the demonstrated prolific inventive genius of the American people. By wise handling of the patent problem and impartial distribution of manufacturing rights, this organization might encourage invention and correct existing inequities.

As another of its important functions, the organization would assist manufacturers to standardize sizes and types of devices. For instance, there is now available a bewildering assortment of bone screws which vary in pitch and depth of thread, in shape and size of head design, and which require at least three types of screw drivers for their insertion. Such lack of uniformity of design increases manufacturing costs, calls for unnecessarily large inventories on the shelves of the distributor, and requires the surgeon and hospital administrator to waste time trying to decide upon the relative merits of a large array of products. Standardization will be of obvious benefit if it is done wisely and through cooperative effort.

Let me here say a word in defense of our friends, the surgical manufacturers, for without them operating rooms would stand deserted and surgeons would be without tools. They are in general skillful, cooperative, and anxious to furnish the surgeon with the materials and devices which he needs. But surgical manufacturing is a relatively small, highly competitive business. Each firm has limited finances and lacks the facilities and personnel necessary for adequate research. The manufacturer buys in small quantities and may be forced to accept materials which are inadequately tested or which are not of the highest quality. The large producers of basic materials, such as steel and plastics, will, I am certain, make every effort to meet the needs of the surgical manufacturers when those needs have been scientifically demonstrated. The organization which I am suggesting can assist manufacturers to obtain standardized materials of uniform quality, at reduced cost.

I have, so far, tried to demonstrate that at present surgical materials and devices are inadequate in many respects and have sketched in outline form a method whereby the present situation might be greatly improved. It is not important that the plan I have suggested be adopted; it is important that the problem be adequately studied, and that steps be taken to improve the present unhappy situation.

I am delighted to be able to tell you that I see many evidences of the willingness of the medical profession and of surgical manufacturers to cooperate in solving these mutual problems. The Executive Committee of The American Academy of Orthopaedic Surgeons have discussed the matter and are willing to consider the possibility of joint sponsorship, with other interested organizations, of a suitable plan. In unofficial conversations, representatives of the surgical manufacturers, the American Medical Association and the American College of Surgeons have evinced an interest in this problem and a willingness to work together in attempting its solution. A joint committee with representatives from each of these groups is being formed to gather evidence, study the alternatives, and make suitable recommendations to the sponsoring organizations. That committee has large responsibilities and I am firmly convinced that it has an unparalleled opportunity to help place surgery on a more scientific basis.

We must use every means at our disposal to lessen the peril of the surgical experiment. In so doing, we are true to the physician's mission in life—"the multiplying of human enjoyments, and the mitigation of human suffering".

CHEMOTHERAPY IN BONE AND JOINT TUBERCULOSIS

Within our lifetime the incidence of tuberculosis of the bones and joints has shown a marked decrease. Thirty years ago a census of the patients in any of the various hospitals for crippled children would have shown a large proportion of the patients to be suffering from some form of tuberculosis of bones or joints. The marked reduction in the incidence of this disease has been due not to chemotherapeutic measures, but to various public-health measures, such as the clean-milk supply, eradication of tuberculous cattle from herds, and the ever-present battle to control the spread of tuberculosis by early recognition and isolation of persons with active tuberculosis.

Tuberculosis remains an important problem, and tuberculosis of bones and joints still exists in all parts of the country. The early diagnosis is often difficult, but is even more important than formerly, because the means to prevent the extensive damage to joints are now available if the disease is recognized early and treated adequately.

Formerly the patient usually first presented himself with an advanced state of the disease that was easily recognized but often difficult to treat. Now early diagnosis is a necessity, and in many instances the tentative diagnosis should be proved by demonstration of the *Mycobacterium tuberculosis* or the typical pathological picture of tuberculosis. Other means of early diagnosis are not accurate enough, and accurate diagnosis must be made before treatment may be applied correctly. Other lesions may simulate tuberculosis, but require an entirely different treatment. Needle biopsies or biopsy of specimens removed at open operations are necessary to establish the diagnosis beyond doubt.

In this issue of *The Journal* are published four papers which summarize the experiences of four groups in treating bone and joint tuberculosis with streptomycin, or streptomycin and para-aminosalicylic acid. Although none of these reports cover observations for more than five years, they do present a fairly accurate summary of the knowledge of this method of treatment to this time. All are agreed that, with the introduction of streptomycin, an important agent has been added to our armamentarium in the treatment of tuberculous bones and joints.

The results of the Veterans Administration survey are compiled from several hospitals; the program was fairly well supervised in all the hospitals and was carried out under as nearly uniform standards as are usually available. It seems evident that streptomycin alone is not so effective as streptomycin combined with standard surgical procedures and that the development of resistance to streptomycin by the organisms is retarded by the use of para-aminosalicylic acid.

The hope that, with early diagnosis and early treatment by means of streptomycin, joints could be salvaged and extensive destruction prevented has not been realized. Further reports on the treatment of early tuberculosis may prove this to be true. It is certainly true, however, that sinuses are more effectively controlled and made to heal, and that operative procedures in the presence of active tuberculous disease may be carried out with much greater safety than before streptomycin was available.

A bolder attack on lesions in their early stages will undoubtedly be developed. Eradication of some foci by surgical means aided by streptomycin seems to be possible. Indeed successful attempts at removal of foci of tuberculosis from the spinal column in the early stages have been reported.

These factors all point toward a much better control of tuberculosis of bones and joints. The severe deformities and severely disabling situations which tuberculosis produces are decreasing and will decrease further. To say that the disease will be eradicated is probably too strong a statement, but such a development now seems possible.

Ralph K. Ghormley, M.D.

STREPTOMYCIN IN BONE AND JOINT TUBERCULOSIS *

BY DAVID M. BOSWORTH, M.D., AND HOWARD A. WRIGHT, M.D., NEW YORK, N. Y.

From the Sea View Hospital, Staten Island, New York

THE GENERAL SITUATION

A few words about the general situation as regards the use of streptomycin for the treatment of tuberculosis should prove a good introduction to the statistics which follow and be convincing of the over-all benefit accruing from the use of this antibiotic.

There were 20,142 patients (Table I) treated at Sea View Hospital from 1941 through 1950. Of these 12,528 were treated before August 1, 1946, and 9,114 after August 1, 1946. Since the bed capacity of Sea View was 1500, this number of patients appears in both groups.

TABLE I

PATIENTS TREATED FOR TUBERCULOSIS

On all Services	1941–1950		20,142
	1941 — August 1, 1946	12,528	
	August 1, 1946–1950	9,114	
Patients treated with streptomycin			2,471
Patients treated without streptomycin			6,643

TABLE II

DEATHS ON ALL SERVICES

Period 1941 — August 1, 1946		3,845
Average	682.8 per year	
Period August 1, 1946 — 1950		2,116
Average	470.2 per year	
Reduction in death rate		31.2 per cent.

The general use of streptomycin on all services at Sea View Hospital began about February 1947. Beginning in August 1946, this material was used in a few experimental cases. The total number treated with streptomycin on all services at Sea View Hospital since August 1946 has been 2,471 cases. During this same period, for various reasons, streptomycin was not used in the treatment of 6,643 patients. The most definite method we have of proving the results is by mortality rates. Before the Second World War the bed services of the Hospital were stabilized at approximately 1,500 and, since all cases referred to Sea View from all other City hospitals are sent there for permanent care, the mortality rate is a definite indication of the results of treatment. The number of deaths (Table II) accruing from the bed capacity at Sea View on all services was as follows: From 1941 to August 1, 1946, there were 3,845 deaths, an average of 682.8 per year. Then, with the advent of streptomycin, for the years August 1946 through 1950 the number of deaths was reduced to 2,116, an average of 470.2 per year. The reduction in deaths on all services, following the use of streptomycin, was 31.2 per cent. Since percentage of deaths is figured on all patients, whether treated with streptomycin or not, the apparent reduction is even more significant.

* Read at the Annual Meeting of The American Orthopaedic Association, White Sulphur Springs, West Virginia, June 23, 1951.

TABLE III

DEATHS ON ORTHOPAEDIC SERVICE

Before the Use of Streptomycin		After Use of Streptomycin in Most Cases	
Year	*No. of Deaths*	*Year*	*No. of Deaths*
1941	19	1946 (first year of streptomycin therapy)	9
1942	30	1947	6
1943	29	1948	5
1944	16	1949	4
1945	17	1950	7

TABLE IV

DEATHS ON ORTHOPAEDIC SERVICE

Period 1941 — August 1, 1946	116 (21.1 per year)
Period August 1, 1946 — 1950	26 (5.8 per year)
Reduction in death rate	72.5 per cent.

The bed capacity of the Orthopaedic Service at Sea View Hospital (of patients under our direct control) has averaged 135 for the last ten years. Again, since these patients cannot be discharged unless they have recovered from the disease, any change in the number of deaths occurring is an indication as to efficacy of treatment. The deaths on the Orthopaedic Service for the years since 1941 are shown in Table III. The deaths in 1941 were nineteen; in 1942, thirty; in 1943, twenty-nine; in 1944, sixteen; in 1945, seventeen; in 1946, nine. The use of streptomycin was begun in August 1946. The deaths in 1947 were six; in 1948, five; in 1949, four; and in 1950, seven. The average number of deaths (Table IV) from 1941 to August 1, 1946, inclusive, was 21.1 per year. The number of deaths from August 1, 1946, to 1950, inclusive, averaged 5.8 per year. Something apparently had happened between these periods to reduce the number of deaths drastically and suddenly. The percentage reduction of deaths on the Orthopaedic Service since streptomycin was first used has been 72.5 per cent. The salvage of patients with severe involvement now brings up new problems of reconstruction. At any rate, with the advent of streptomycin, a drastic change took place in the institution, not only as to the number of deaths but

TABLE V

PATIENTS TREATED ON ALL SERVICES AUGUST 1, 1946 — 1950

	No. of Patients	Deaths	
		No.	*Per cent.*
Treated with streptomycin	2,471	275	11.1
Treated without streptomycin	6,643	2,117	31.9
Reduction in death rate			65.3

TABLE VI

PATIENTS TREATED ON ORTHOPAEDIC SERVICE — AUGUST 1946 — 1950

	No. of Patients	Deaths	
		No.	*Per cent.*
Treated with streptomycin	355	21	5.9
Treated without streptomycin	25	5	20
Reduction in death rate			80

TABLE VII

Deaths on Orthopaedic Service among Patients not Receiving Streptomycin		5
Causes of Death		
Multiple osseous lesions	2	
Osseous and renal lesions	1	
Osseous and gastro-intestinal lesions	1	
Osseous and pulmonary lesions	1	

also as to the comfort and condition of the patients; of this fact the death rate is only one indication.

One fact in itself denotes the increased general comfort of the patients. In previous years, carbolization of sinuses was a daily routine; during the past six months, not a single sinus has needed carbolization. Actually our wards are being depleted by recovery of patients faster than admissions take place.

Since the institution of streptomycin during the past four and a half years (Table V), there have been 2,471 patients treated with this drug on all services at Sea View Hospital: of these 275 died (11.1 per cent.). There were 6,643 not treated with streptomycin and of these 2,117 died (31.9 per cent.). Thus, since the advent of streptomycin, there has been a 65.3 per cent. drop in mortality for patients on all services.

During this same period (Table VI) there have been 355 patients treated with streptomycin on the Orthopaedic Service and of these twenty-one have died, 5.9 per cent. There were twenty-five not receiving streptomycin and of these five died (20 per cent.). The death rate among patients on the Orthopaedic Service, therefore, has shown an 80 per cent. drop since the advent of streptomycin therapy.

Since the Medical Service has used streptomycin in conservative doses (at first up to ninety grams and recently up to thirty or forty grams only), and the Orthopaedic Service has continued the use of streptomycin indefinitely until recovery was secured and the patient was discharged or death occurred, it would seem that, if adverse effects were to be shown to accrue from the use of this drug, they would appear in the list of deaths on the Orthopaedic Service. We have carefully inquired into the causes of death of the twenty-one orthopaedic patients who had had streptomycin. We have contrasted them with the causes of death of the five who died during this same period without having had streptomycin.

The five patients (Table VII) who had no streptomycin and died were admitted in desperate condition and in the early period of use of this drug. Because their infection was overwhelming, we were convinced at that time that the use of streptomycin would not help. Two deaths were due to multiple widespread osseous lesions accompanying other conditions, which were moderately active, such as a pulmonary fibrosis. One patient died of a severe tuberculous renal lesion, another of a severe tuberculous gastro-intestinal lesion, and the fifth of an advanced tuberculous pulmonary lesion. The deaths of all five patients who had not had streptomycin used occurred late in 1946, a period when only

TABLE VIII

Deaths on Orthopaedic Service Among Patients Treated with Streptomycin			21
Within six weeks of admission	5		
More than six weeks after admission	16		
Causes of Death			
Osseous lesions	5	Cirrhosis of liver	1
Meningitis	3	Carcinoma	1
Amyloid disease	2	Hemorrhage	1
Cardiac failure	2	Pulmonary disease	1

experimental amounts of the drug were available, and these were used for patients who we considered had some chance to survive.

Twenty-one deaths (Table VIII) occurred during the past five years in patients who had had some amounts of streptomycin. We consider a death within six weeks of admission to Sea View Hospital as one occurring before the full effect of streptomycin can be secured. Five died within this six-week period. Four of these deaths were recorded as from extensive osseous disease complicated by inanition, cachexia, and sinuses. One patient died following an occipitocervical fusion.

Sixteen deaths occurred after the six-week period of use of streptomycin. Of these sixteen deaths, five were from advanced osseous disease with sinuses, persisting cachexia, and other tuberculous involvement, such as pulmonary or renal; three were due to tuberculous meningitis; two to amyloid disease with multiple tuberculous foci and draining sinuses; two to cardiac failure; one to cirrhosis of the liver and portal obstruction; one to adenocarcinoma of the rectum (although the patient was still in good condition as regards the tuberculous lesions); one was from a sudden severe pulmonary hemorrhage, and one from bilateral caseous tuberculous pulmonary disease.

There were no deaths accompanied by severe gastro-intestinal symptoms, renal lesions, or skin lesions, indicating toxicity from streptomycin—this despite the fact that up to 1,035 grams have been used on occasion and the employment of 500 grams or more is not unusual.

TABLE IX

ADDITIONAL CLOSED LESIONS PRESENT IN PATIENTS WITH OPEN LESIONS

No. of lesions	39		No. of patients	32	
Distribution of lesions:					
Spine	21	Rib	2	Cartilage	1
Sacro-iliac joint	3	Meninges	2	Tarsus	1
Knee	3	Ankle	1	Wrist	1
Elbow	2	Scapula	1	Viscera	1

TABLE X

CLOSED LESIONS PRESENT IN PATIENTS WITH OPEN LESIONS

No. of lesions	39	No. of patients	32
	Surgery used in	37	
	Surgery not used in	2	

PROBLEMS CONSIDERED

Four problems will be considered. These are not all which arise, but are those of interest at this time in view of preceding papers or exhibits, and in an attempt to clarify findings or opinions arising from them.

Problem 1: Will streptomycin alone (that is, without surgery) check or heal closed lesions?

Problem 2: Should abscesses be drained? Should they be closed or left open thereafter?

Problem 3: Where sinuses are present, what permanency of closure results with the use of streptomycin?

Problem 4: Does prolonged use of streptomycin give disastrous results, either from toxicity of the drug or development of resistance in the organisms?

Problem 1: Will the use of streptomycin check or heal closed lesions?

In order that conclusions drawn may be valid in any series of cases under estimation, it is necessary to have absolute proof that a closed lesion is the result of infection with

tuberculosis. We have, therefore, limited ourselves to closed lesions present in bones or joints among the ninety-six patients previously reported [1] who were treated with streptomycin for a proved tuberculous bone or joint lesion with sinus formation. Any other closed lesion among these patients which provided the typical findings of tuberculosis we are, for this study, considering tuberculous in etiology. In many of these patients, surgery was required at a later date, which permitted examination of tissue from many of these foci. In no such instance among these closed lesions was it necessary to revise our diagnosis. Since this is so, we can well assume that the other lesions, which did not require surgery permitting section of involved tissue,were likewise tuberculous. Therefore, we feel we can justly draw conclusions on these additional closed lesions and their response to streptomycin.

Among the ninety-six patients (Table IX) with a proved open focus, there were thirty-nine additional foci in bones or joints, without sinuses, which conformed to all criteria. These thirty-nine foci were present in thirty-two patients. The lesions were

TABLE XI

TREATMENT OF ABSCESSES

Abscesses incised			21
In patients treated with streptomycin		18	
In patients not given streptomycin		3	
Deaths	2		
Incision open	1		

TABLE XII

RESULTS OF TREATMENT OF ABSCESSES

Abscesses incised in patients treated with streptomycin			18
Abscesses sutured		3	
Reopened	2		
Closed	1		
Abscesses not sutured		15	
Patient died	1		
Abscesses healed	3		
Definitive surgery required	11		

found in twenty-one spines, three sacro-iliac joints, three knees, two elbows, two ribs, one ankle, one scapula, one wrist, the meninges in two patients, costal cartilage in one patient, and tarsals in another, as well as in one patient with enteritis. Eleven of these closed lesions later at operation were proved to be tuberculous; these were lesions in which the diseased area was later entered; they involved an ankle, a scapula, two ribs, three knees, as well as the costal cartilage in one case, and included the patient with enteritis and two patients with meningitis. All of the closed lesions of the spine, sacro-iliac and knee joints required surgical ankylosis. In only two (Table X) of the thirty-nine closed lesions among these patients, which conformed to a diagnosis of tuberculosis, was surgery not used. One patient with a tarsal lesion died; this patient is reported among those who died after six weeks' treatment with streptomycin. One patient with a wrist lesion had no surgery.

It is, therefore, apparent that, despite the use of streptomycin, most patients with closed lesions, whose findings are consistent with a diagnosis of tuberculosis, eventually come to stabilizing operations or other surgery, if followed long enough, either because of activity of the disease or because of bone or joint destruction already present.

TABLE XIII

RESULTS IN TUBERCULOUS PATIENTS WITH SINUS FORMATION

Patients with bone or joint lesions with sinuses		96
Patients followed		86
Lesions healed and patients well	74	
Patients at home and well	72 (83.7 per cent.)	
Lesions not healed or recurring	9 (10.5 per cent.)	
Patients who died with sinuses closed	3	
Patients who died with sinuses open	5	
Patients still living with sinuses open	4	

Problem 2: Should abscesses be incised under streptomycin control, and closed or left open?

Under this heading we will not consider biopsies done as a clean procedure, where an abscess was not present, even though tuberculous tissue was transsected. Neither will we consider cases where incision was done, if definitive surgery—such as resection of a part or all of a bone or joint—was done at the same operation. We shall only consider cases in which incision of the abscess was done without definitive surgery, evacuation of the abscess was accomplished, and either closure was performed primarily or the incision was left open to drain. This strictly limits us, and we have been able to find but twenty-one such cases to report (Table XI). Of these twenty-one patients, only eighteen were protected with streptomycin. Of the three unprotected, two died with drainage and cachexia. In the other patient, the abscess healed, reopened, and later closed after the patient was given streptomycin.

In eighteen patients (Table XII) treated with streptomycin, simple incision of the abscess was done; in fifteen the incisions were left open and allowed to drain and in three the incisions were closed primarily. Of the three whose incisions were closed primarily, spine fusion was necessary in two and the incisions which had broken down eventually closed again. One whose incision healed *per primam* later had a spine fusion for vertebral collapse.

In fifteen patients under streptomycin therapy, the abscesses were incised and left open to drain. Their course warrants brief description.

One patient with tuberculosis of a knee was admitted to Sea View Hospital under streptomycin therapy with a severe suppuration from several apparent slash incisions which represented the original incision of the abscess. His condition appeared hopeless. Under continued streptomycin, healing on one side was gained, and a hemifusion was carried out on that side. Healing occurred on the opposite side nine months later. The patient was discharged, ambulatory and with the lesion healed, and it has remained healed.

Another patient had an evacuation of a sternal abscess under streptomycin therapy. This abscess ulcerated and finally closed under treatment with seventy grams of streptomycin.

One died with draining incision still open, gradually progressive marked inanition, secondary infection, and moderately advanced pulmonary tuberculosis.

In one patient, a young girl, admitted to us in excellent condition, a small incision closed under treatment with seven grams of streptomycin (in seven days). Spine fusion was done. The streptomycin was continued for a total of 371 grams, and the girl has had no recurrence since that time.

In all of these patients who have incisions left open, the speed of closure is unpredictable. The appearance of the wound has much less influence on the prognosis than does the general appearance or cachexia of the patient. For instance, one patient was sent to us who had had an incision while under streptomycin treatment but thereafter was apparently not improving. He had extremely severe draining sinuses, but, aside from these, his general condition was good. Prompt stabilizing surgery accompanied continued use of

TABLE XIV

COMPLICATIONS RESULTING FROM STREPTOMYCIN THERAPY

Patients with prolonged treatment with streptomycin		86
Patients who became deaf	5 (5.8 per cent.)	
All patients on Orthopaedic Service treated with streptomycin		355
Patients who became deaf	5 (1.1 per cent.)	
Incidence of vertigo or ringing ears	26.7 per cent.	
Incidence of headache	2.3 per cent.	

streptomycin. He had had a spine fusion, which could not in that short time be considered to have become solid; yet, after he had received sixty-five grams of streptomycin, his sinuses healed. After streptomycin had been continued for a total of 362 grams, he was finally discharged in excellent condition. None of these patients who had abscesses incised and left open were so fortunate as to be found with healed wounds when the dressings were first removed.

In the other nine patients who had incisions of abscesses left open, all the incisions have healed and have remained healed following surgery and continued use of streptomycin. The longest period before healing was achieved with surgery was 112 days. Streptomycin given during that period amounted to 112 grams and was continued thereafter for varying periods.

Incisional surgery to drain abscess material about weight-bearing joints under the protection of streptomycin may temporarily (for a few months) give the impression of control of the situation without definitive surgery. Where no joint is involved, and an osteomyelitic lesion is present (as in the sternal case previously mentioned), prolonged use of streptomycin may achieve a satisfactory end result. Where a weight-bearing joint has been invaded, the grinding process produced by motion or impaction of normal bone and necrotic fragments seems sure to light up the original infection, causing continued disability, unless protection is provided by arthrodesis. The long-range view based upon experience with large numbers of tuberculous patients who have been unable to escape surgery is necessary for an accurate clinical evaluation. Even though an abscess in a spine lesion is drained or incised and closed, progression of the destructive process, the angulation, and the disability still demand surgical fixation.

Problem 3: Where sinuses are present, what permanency of closure results from the use of streptomycin and surgery?

Of the ninety-six patients previously reported (Table XIII) who had a proved tuberculous bone or joint lesion with sinus formation, we have been able to follow eighty-six to the present. Nine of these patients either now have a sinus or have had a recurring sinus from time to time; this represents a failure rate of 10.5 per cent. in such cases to date. The causes of failure have remained essentially the same as reported in the previous paper. Several of the patients previously reported as failures have, with reconstructive surgery, been healed and remained healed. A certain number still remain unhealed. Uncollapsed bony pockets, impossible to reach safely with surgery, are present in some.

Three patients of this group have died, with their sinuses closed. Two died with intra-abdominal carcinoma, and the third patient succumbed of tuberculous meningitis.

Five patients died with sinuses still draining. Two of these died of tuberculous meningitis, one of an aplastic anaemia, one of amyloid disease, and one patient of diffuse lympho-hematogenous tuberculosis with advanced bilateral caseation.

The average follow-up period on these patients has been three and a half years. After this period of time, only four patients are living who have had continuous drainage of their sinuses or reopening of the sinuses from their original osseous source. This gives one pause to think.

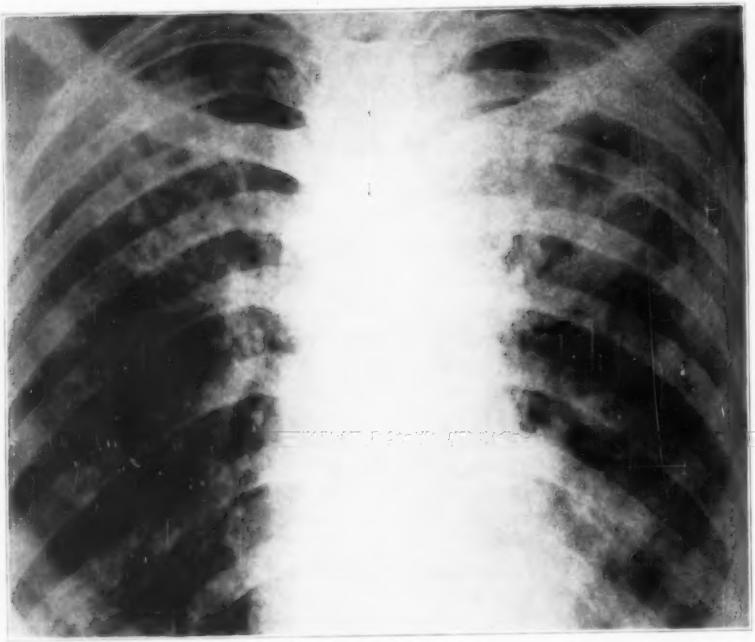

FIG. 1-A

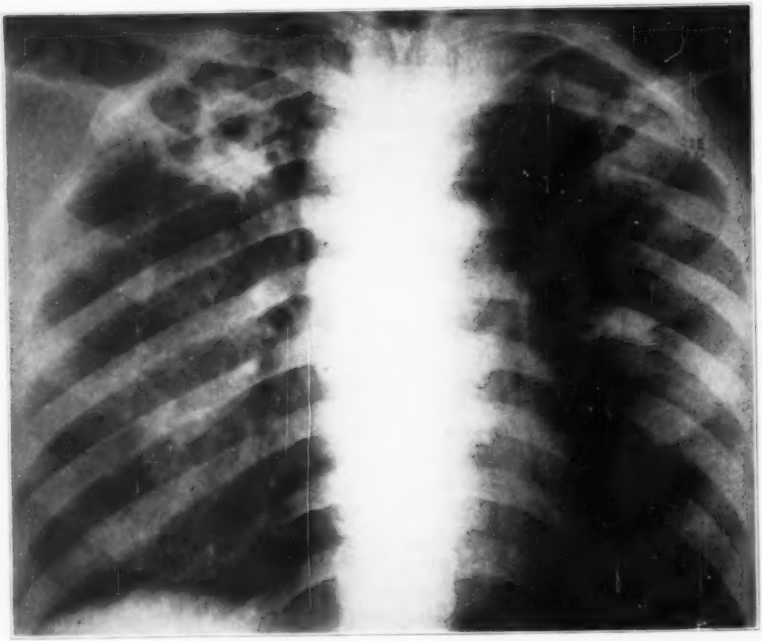

FIG. 1-B

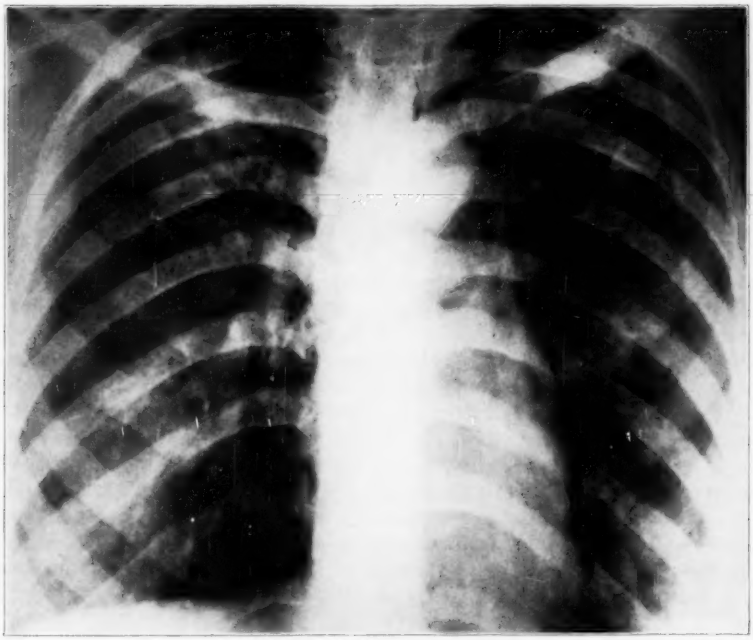

FIG. 1-C

Figs. 1-A to 1-C: Frequently, healing of severe chest involvement occurs with the prolonged course of streptomycin and bed rest necessary for orthopaedic surgical care. The roentgenograms show a severely involved chest at original examination (Fig. 1-A), after two years of streptomycin (Fig. 1-B), and after three years of streptomycin (Fig. 1-C), respectively. Note the clearing of the parenchyma and healing of the cavity in Fig. 1-C.

Of these eighty-six patients (Table XIII) whom we have been able to follow, out of the original group of ninety-six, seventy-four have their sinuses healed; these have remained healed since they closed under streptomycin therapy. All except two of these seventy-four patients have been discharged from the hospital. These two are still in the institution for lesions other than those causing sinus formation; they are in good condition, with good outlook. Seventy-two of the eighty-six patients whom we were able to follow have recovered, are healed, in good condition, at home, and essentially normal in their activities, so far as disabilities due to arthrodesing procedures will permit. For the purposes of this follow-up, therefore, 83.7 per cent. recovery rate has been provided for these extremely involved and difficult cases by the use of streptomycin combined with proper surgery.

Problem 4: Does prolonged streptomycin give disastrous results, with complications directly due to streptomycin or to the development of resistance in the organisms?

There are a total (Table XIV) of eighty-six patients on our wards at this time at Sea View Hospital who have been continuously under streptomycin therapy. These are the patients requiring prolonged treatment; sixty-eight are adults and eighteen are children. Patients who have had streptomycin, but in whom the antibiotic has been discontinued or its use interrupted at any time, have not been included.

Absolute or essentially complete deafness has occurred in five patients,—three children and two adults (5.8 per cent.). One child who had tuberculous involvement of the spine from the second cervical throughout the thoracic and lumbar regions to the sacrum had surgical fixation of the whole area satisfactorily done in stages. Fusion is

now solid without pseudarthrosis, with complete clinical recovery. The child is in excellent condition. At 485 grams of streptomycin (970 days) deafness was noted, and streptomycin was stopped.

The second child, with a tuberculous knee, had an arthrodesis done, and at 242 grams (within 484 days) of streptomycin deafness developed. Streptomycin was stopped. The third child was admitted with an active pulmonary lesion, a positive sputum, and a spine lesion. Arthrodesis of the thoracic area was satisfactorily accomplished and under continued streptomycin therapy the chest cleared. At 274 grams (within 548 days) deafness was found; streptomycin was stopped. The spine has shown no collapse; fusion is present; her chest condition has completely resolved; her sputum is negative; and her general condition is excellent. Two of these three children would probably have died, according to our old statistics, except for the use of streptomycin. We feel that deafness can be well accepted in exchange for a living, healthy child.

Two adults became deaf. One had multiple osseous and joint lesions with marked cachexia and multiple draining sinuses from several lesions; he became deaf on 365 grams (365 days). Despite his deafness, streptomycin has been continued to a total now of 723 grams. The patient has remained in a condition equivocal as far as recovery is concerned, but would long since have died according to our previous observation and statistics. He may yet recover, although, if recovery occurs, it will be only after considerable additional surgery and continued antibiotic treatment. The second adult has a spine lesion which has not been arthrodesed because of her previous poor general condition and severe renal complications. One kidney has been excised and the other kidney is badly involved with a fibrotic lesion which has been controlled with streptomycin. Her kidney function is less

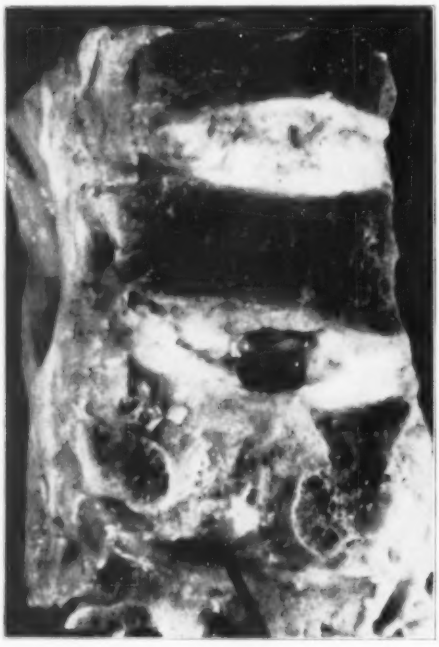

FIG. 2-A

FIG. 2-B

Sterilization of thick-walled abscesses and caseous pockets such as those shown here, with final shrinkage, collapse, and fibrosis, requires months or years. Protection with streptomycin is necessary during this time.

than 10 per cent. She became deaf at 200 grams of streptomycin; treatment so far has been carried on to 255 grams. Her condition has improved so that she appears normal. Spine fusion can now be done.

There were no other patients on the Orthopaedic Service at Sea View Hospital in whom deafness has developed. Since 355 patients on the Orthopaedic Service have been treated with streptomycin, the percentage of deafness occurring with its use, often in large quantities, is actually only 1.1 per cent. However, in view of the record of salvage as shown, we will accept the 5.8 per cent. chance of deafness occurring with *prolonged* treatment in orthopaedic patients with severe involvement of tuberculosis.

The occurrence of deafness seems to be rather sudden. A complaint of ringing in the ears is generally present for a variable period before it occurs, and then one day, on examination of the patient, he is found unable to hear and for the first time deficiency is recorded. When deafness of any extent occurs, it seems to be permanent. Where deafness is incomplete, some improvement may take place in situations where the condition of the patient and the tuberculous lesion permit discontinuance of the drug.

We have included vertigo and ringing in the ears as one complication. In most cases they seem to accompany each other. Such vertigo as is present has not become extreme, in our experience, and has subsided with discontinuance of the drug after final treatment. This complication (vertigo or ringing in the ears, or both) occurred in 26.7 per cent. of the patients (both children and adults). Headache occurred in 2.3 per cent. of the patients and disappeared on reduction of the drug.

Abscess formation at site of injection has been seen on only one occasion. Streptomycin injections at Sea View Hospital are given and recorded by a separate trained team who circulate throughout the institution. Over 23,000 injections have been given to these eighty-six patients alone, with only this one abscess formation. We believe this a high tribute to our nursing personnel.

A transitory dermatitis occurred in only one of these eighty-six patients and disappeared with continuance of the drug at a lower dosage.

Idiocy occurred in one child who had a proved tuberculous meningitis and was treated with streptomycin. He recovered from his meningitis and left Sea View a permanent imbecile. We believe that meningitis and not streptomycin caused the mental changes.

No digestive disturbances related to streptomycin therapy have been seen. Occasional digestive disturbances have occurred in the patients, but on continuance of streptomycin at the same dosage these have disappeared. We feel that no group of patients hospitalized over a period of many months, at a City institution where food of all sorts is brought to them by their visitors, under cover and without permission, can be expected to continue without such disturbances.

Exacerbation of the disease either locally at the bone or joint lesion or in accompanying chest or kidney lesions, either related or unrelated to streptomycin, has not occurred.

As a matter of fact, on numerous occasions chest lesions not supposed to improve with streptomycin, or actually believed to be made worse by development of resistance of tubercle bacilli to streptomycin, have been shown to improve on the prolonged course of streptomycin given on the Orthopaedic Service for the osseous and joint lesions (Figs. 1-A, 1-B and 1-C). One of these patients showed bilateral cavitation and sputum which was markedly Gaffky positive. She had tuberculosis of the sacro-iliac joint and the joint was fused. No drainage occurred. Streptomycin was instituted before fusion and was carried on continuously. She remained on our wards during the prolonged period necessary for ankylosis of her sacro-iliac joint to become solid. During all of this time streptomycin was automatically continued by us to protect her during the period of consolidation of the sacro-iliac joint. One year after institution of the streptomycin therapy, the chest condition showed slight improvement, while the sputum had become negative. It was only two years following the institution of the streptomycin treatment that the true change in the

chest became thoroughly apparent with resolve of the tuberculous process and disappearance of the cavities, leaving behind only slight scarring in the parenchyma of the lung. This patient had no medical treatment throughout this time. Collapse therapy had been attempted before we received her and had failed. She had been considered incurable as to the chest condition.

It is our feeling that, with fibrotic lesions in the chest, it well may be shown that a prolonged period is required for the body to resolve the fibrosis, absorb the abscess products, and heal the lesion with contracted scarring. We would feel that this supposition paralleled that of the Orthopaedic Service in which we know that short periods of bodily healing cannot possibly heal deep sinuses, such as are shown to exist in a severe tuberculous spine, with fibrotic walls and massive distention. To absorb the detritus of a fibrous encapsulated abscess as in a large psoas abscess, or to heal a large vertebral sinus tract (Figs. 2-A and 2-B) may take years. We have often shown split sections denoting the gross pathology present in such cases, and similar sections of the lung have often been made available for study elsewhere.

We no longer have the feeling of defeat which we formerly had even when a patient is admitted with multiple osseous lesions, positive pulmonary lesions, damaged kidneys, and in a cachectic state. Although some of these patients will die despite care, many of them will recover with prolonged streptomycin treatment and adequate surgery. No one can tell in advance which patient will recover and which will die, and a prolonged trial of streptomycin is justified in our opinion, without relation to development of resistance of the tubercular organism. The streptomycin does much more than delay development of the tubercle bacillus. It has a direct action on the metabolism of the patient and withholds secondary invaders both within and without the blood stream.

We have not employed para-aminosalicylic acid, in view of the many reports that it was an adjuvant to streptomycin but not in and of itself of definitive value. Neither have we used tibione (thio-semicarbazone). We would feel that where streptomycin was used with improvement in orthopaedic cases with para-aminosalicylic acid or tibione, such improvement should be credited to the streptomycin, the known beneficial active ingredient of the combination.

CONCLUSIONS

1. Streptomycin has tremendously influenced and improved the treatment of bone and joint tuberculosis.

2. Surgery for stabilization of damaged joints, excision of sequestra, and drainage of abscesses, seems to be still demanded as in the days before the use of streptomycin, but it is safer and much more efficient.

3. Complications arising from the use of streptomycin are fairly innocuous and thoroughly acceptable, in view of the disasters which occur without its employment.

1. Bosworth, D. M.; Della Pietra, A.; and Farrell, R. F.: Streptomycin in Tuberculous Bone and Joint Lesions with Mixed Infection and Sinuses. J. Bone and Joint Surg., **32-A:** 103-108, Jan. 1950.

TUBERCULOSIS OF THE BONES AND JOINTS

With Special Reference to the Influence of Streptomycin and the Application of Radical Surgical Techniques to Certain Effects and Complications of the Tuberculous Lesion*

BY EDWARD T. EVANS, M.D., MINNEAPOLIS, MINNESOTA

In the treatment of bone and joint tuberculosis tradition and past experience have been particularly evident in establishing "standards", or certain dicta, the continued acceptance of which, in the light of present developments, has thwarted progress and doubtless condemned some patients to a fatal outcome or at best to a long-suffering convalescence, economically and physically crippling in its end results.

This study is a plea for a re-evaluation of the problem, an almost complete reversal of thought, arrived at in certain groups of cases. Experience with these cases would seem to disprove four well established dicta.

Dictum I. The surgical attack on tuberculosis, even though the disease is progressively destructive locally, must await the stabilization of the infection as a whole as evidenced by a favorable response to rest, subsidence of the systemic reaction, and stability of the sedimentation rate.

If one recognizes that tuberculosis is a systemic disease requiring a sanatorium regimen and the combined efforts and team work of a well trained staff for its best control, one will still disagree with this dictum in view of the newer concepts of treatment. Only examples such as those presented in the Case Reports will lead the conservative members of the staff to the newer point of view.

Dictum II. In disseminated tuberculosis which is manifest in multiple lesions that are gross in nature, surgical measures are contra-indicated until the disease seems stabilized.

We know the disease is microscopically disseminated in any event and is always systemic in nature. What magic formula lies in these gross manifestations that preclude early surgical procedures directed against lesions the persistence of which only debilitates the patient further? Early arrest or eradication of a lesion should and will improve the patient's general status. Miliary spread was justly feared in the past; today, with antibiotics, its occurrence is minimized.

Dictum III. The presence of abscess at the site contemplated for surgery is a contra-indication to arthrodesis or other procedures and especially to the use of bone grafts.

To this the argument is advanced that excision of the abscess, either as a preliminary step or at the time of arthrodesis or of excision, will be eminently successful. Is arthrodesis of the knee with associated bone-grafting and internal (nail) fixation, involving as it does surgery within an extensive abscess, so different from arthrodesis in the presence of abscesses of the hip, shoulder, or spine? Judicious extirpation of the abscess, administration of antibiotics, and adequate fixation or excision overcome these complications in a high percentage of cases and lead to earlier rehabilitation of the patient.

Dictum IV. The development of serious abscesses and sinuses, either spontaneous or postoperative, represents a complication which is often insurmountable and may doom the patient to gradual decline and death from amyloidosis.

This view has been somewhat tempered by the adjunct use of streptomycin but, I fear, with an all too frequent disregard of the possibilities of established surgical procedures.

This last dictum is frequently alluded to in statistics as the cause of failure of this

* Based on a paper read as part of a Symposium presented at the Annual Meeting of The American Orthopaedic Association, White Sulphur Springs, West Virginia, June 23, 1951.

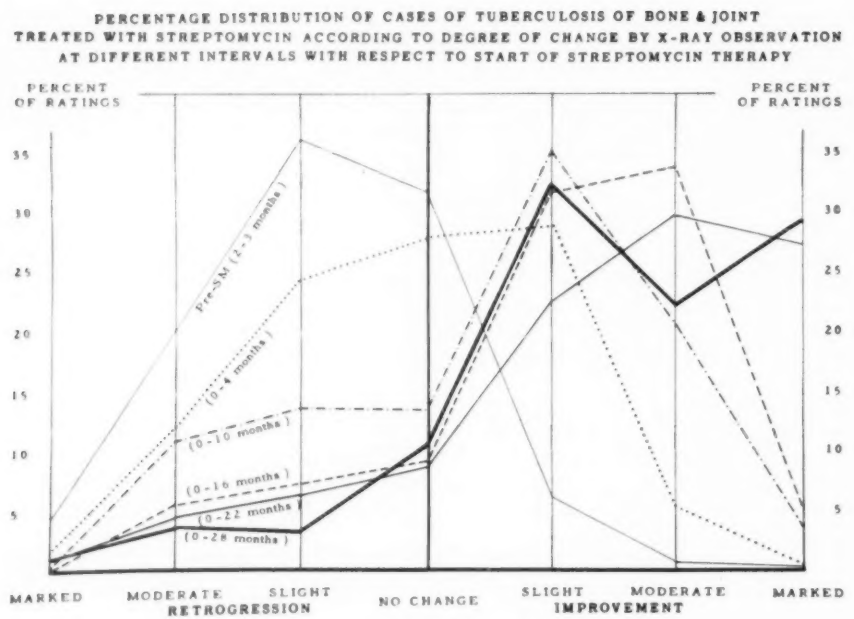

CHART I

or that surgical procedure. Its acceptance has led to the disrepute into which have fallen many surgical methods of attack on the tuberculous lesion.

In 1936 and 1937, regardless of this fourth dictum and without the aid of the sulfonamides or antibiotics, the radical *excision* of sinus tracts was practised by the author along lines which have since become popularly known as the primary débridement and secondary closure of wounds so extensively carried out in war surgery. Once established, the tubercle bacillus thrives on fascia, synovia, serous membrane, and relatively inert tissues. With the exception of primary tuberculosis of the myocardium, I have not seen or heard of tuberculosis of the muscles. The bacillus also does not thrive in areas of rich blood supply or fresh granulations. Given half a chance, the local tissues will heal if indolent scar is excised, if the nidus of the infection is extirpated or controlled, and if the principles of early secondary closure are carried out. This was true before the advent of streptomycin and is certainly true at this time. This is why, in the author's judgment and experience, the combined use of *incision*, drainage, and streptomycin fails in a fair percentage of cases. Surgical *excision* of the tract, scar tissue, and the nidus of infection, with adjunct use of streptomycin and early secondary closure before scar formation, is the ideal for which we must strive.

Some of the old ideas on the surgery of bone tuberculosis need revision; the new ideas may, with modern techniques, anaesthesia, and adjunct antibiotics, be safely carried out. Cases are here presented which illustrate the management of the more severe complications by adequate extirpation, débridement, and early closure; the principles are the same as those now applied in war wounds and compound fractures. A plea is made for early joint stabilization in those cases which are obviously involved by rapid osteolysis through tuberculous infection. While complications may develop, they will be less likely to occur, and, if they do, they may be more directly attacked with greater assurance of ultimate success.

Such ideas might fall upon deaf ears were it not possible to present substantiating

PERCENT OF RATINGS SHOWING IMPROVEMENT BY X-RAY OBSERVATION IN NON-STREPTOMYCIN-TREATED CASES OF TUBERCULOSIS OF BONE & JOINT

(Review of September 17-18, 1949)

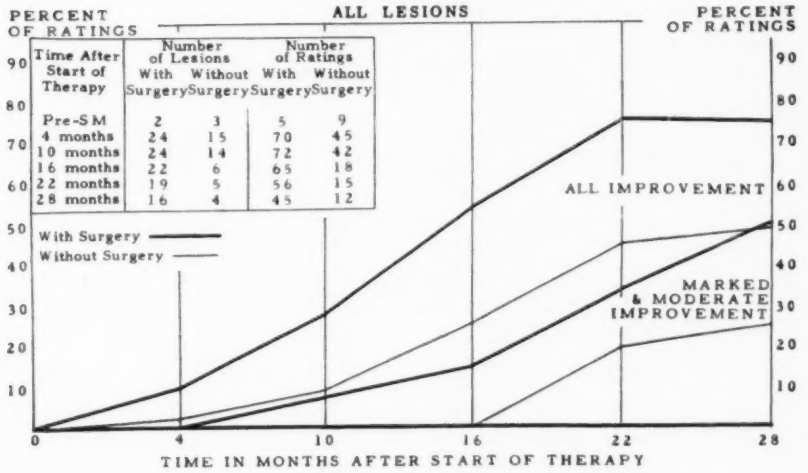
PERCENT OF RATINGS
ALL LESIONS
PERCENT OF RATINGS
Time After Start of Therapy
Number of Lesions With Surgery
Number of Lesions Without Surgery
Number of Ratings With Surgery
Number of Ratings Without Surgery
Pre-SM 2 3 5 9
4 months 24 15 70 45
10 months 24 14 72 42
16 months 22 6 65 18
22 months 19 5 56 15
28 months 16 4 45 12
With Surgery
Without Surgery
ALL IMPROVEMENT
MARKED & MODERATE IMPROVEMENT
0 4 10 16 22 28
TIME IN MONTHS AFTER START OF THERAPY

CHART II

evidence of the relative merits of various methods of treatment. It was the author's privilege to be one of a jury with Dr. Ghormley and Dr. Bickel in conducting the 1948 and 1949 reviews of the effects of streptomycin in bone and joint tuberculosis and, through

PERCENT OF RATINGS SHOWING IMPROVEMENT BY X-RAY OBSERVATION IN STREPTOMYCIN-TREATED CASES OF TUBERCULOSIS OF BONE & JOINT

(Review of September 17-18, 1949)

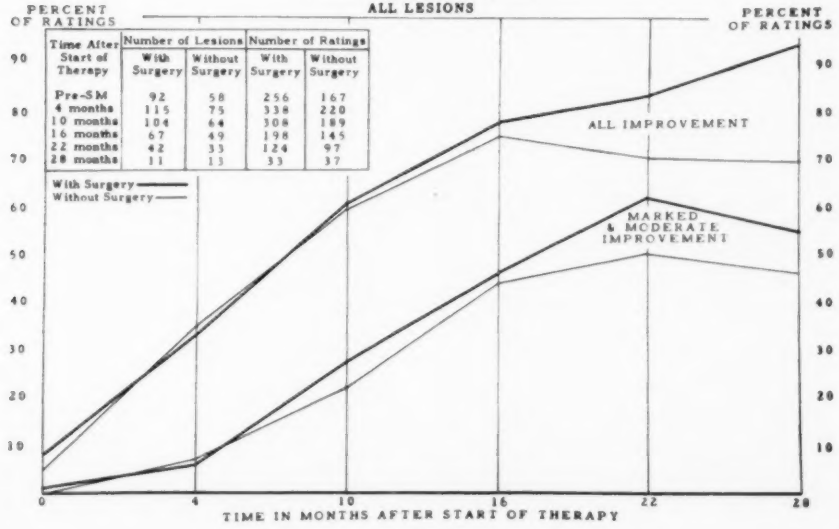
PERCENT OF RATINGS
ALL LESIONS
PERCENT OF RATINGS
Time After Start of Therapy
Number of Lesions With Surgery
Number of Lesions Without Surgery
Number of Ratings With Surgery
Number of Ratings Without Surgery
Pre-SM 92 58 256 167
4 months 115 75 338 220
10 months 104 64 308 189
16 months 67 49 198 145
22 months 42 33 124 97
28 months 11 13 33 37
With Surgery
Without Surgery
ALL IMPROVEMENT
MARKED & MODERATE IMPROVEMENT
0 4 10 16 22 28
TIME IN MONTHS AFTER START OF THERAPY

CHART III

PERCENT OF RATINGS SHOWING IMPROVEMENT BY X-RAY OBSERVATION
IN STREPTOMYCIN & NON-STREPTOMYCIN TREATED CASES
OF TUBERCULOSIS OF BONE & JOINT
According to Employment of SM & Surgery
(Review of September 17-18, 1949)
ALL DEGREES OF IMPROVEMENT
ALL LESIONS

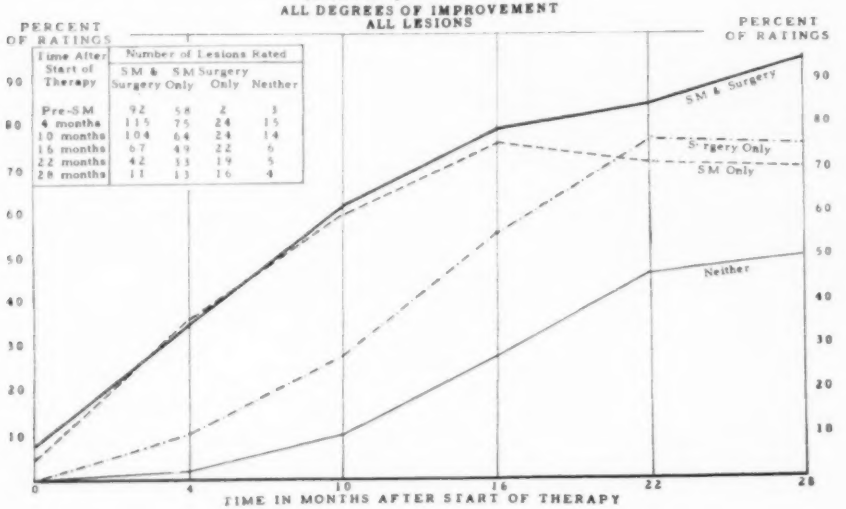

CHART IV

association with Glen Lake Sanatorium, to supply a comparable series of cases not treated with streptomycin.

The statistical material comprises forty-eight pages of tables, graphs, and comments contained in the Minutes of the Eighth Streptomycin Conference[2]. Limitations of space do not permit presentation here in detail, but the chief observations may be summarized.

FIG. 1-A
April 1947

FIG. 1-B
December 1951

Two hundred and thirty-eight cases were reviewed. Of these, forty-two were not treated with streptomycin and are included for control purposes. Streptomycin is not a panacea; 10 to 15 per cent. of the cases showed regression of various degrees during administration of the drug (Chart I).

FIG. 2-A
October 1950

FIG. 2-B
February 1951

FIG. 3-A
May 1949

FIG. 3-B
December 1950

FIG. 4-A
May 1948

FIG. 4-B
July 1948

Without streptomycin improvement occurred slowly under a well controlled sanatorium regimen and was increased only moderately by adjunct operative intervention. Surgery is an effective method of treatment directed toward ultimate stabilization of the process (Chart II).

Streptomycin initiates an early improvement, but such improvement may not be maintained and here, too, surgery is an effective method of treatment directed toward ultimate stabilization of the process (Chart III).

The combined use of surgery and streptomycin gave best results, while a sanatorium regimen alone was most disappointing. In the author's opinion this is one of the most potent arguments for judicious surgery.

There is no substitute for time under a

FIG. 5-A
April 1947

FIG. 5-B
January 1949

FIG. 6-A
August 1949

FIG. 6-B
March 1950

FIG. 6-C
April 1950

FIG. 6-D
June 1950

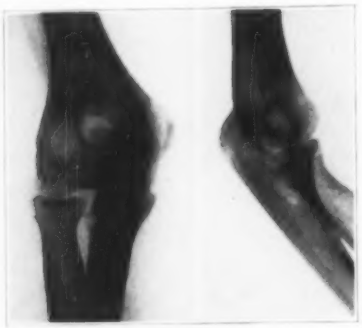

FIG. 7-A
October 1949

FIG. 7-B
May 1951

FIG. 7-C
July 1949

FIG. 7-D
March 1951

FIG. 7-E
July 1949

FIG. 7-F
May 1951

FIG. 8-A
January 1951

FIG. 8-B
May 1951

controlled sanatorium or similar regimen, and the review shows that twenty-two to twenty-eight months is necessary to estimate reversibility of the process. Surgery and streptomycin, singly or combined, are adjuncts of therapy (Chart IV).

The role of streptomycin as adjunct therapy in tuberculosis is well established. However, every case must be carefully evaluated in staff conference. Injudicious use of the antibiotic, which makes the organism resistant to its effect, may preclude its use at a more critical time.

The effect of streptomycin upon pure synovial involvement, as reported by Ghormley and Bickel, is often miraculous. For such cases, after careful evaluation and if no other serious involvement is found, early streptomycin therapy seems justifiable. A false sense of security must not, however, be encouraged until a long period of observation has elapsed.

Critical periods in the patient's over-all course of treatment should be anticipated in clinical conferences. If streptomycin therapy is reserved for these serious episodes, the patient will receive the greatest benefit from specific antibiotic therapy.

A course of streptomycin therapy is often of relatively short duration—seldom more than three months—although there is recent evidence which would seem to favor the use of smaller doses over longer periods of time (streptomycin, one gram twice a week, with para-aminosalicylic acid, four grams daily). Tuberculosis in all its forms is reversible, particularly bone tuberculosis. However, no false sense of security is justified on the basis of streptomycin therapy. The criteria for the arrest of the lesion must be satisfied as heretofore.

Short repeated courses of streptomycin, totaling thirty to sixty days, may be given as necessary in conjunction with subsequent or repeated surgical procedures, even though resistance to the drug has developed. Its favorable effect on the general well-being of the patient and the reduction of complications, local and general, is a well recognized clinical observation.

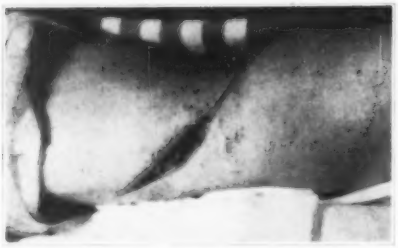

FIG. 9-A
Abscess of psoas on right
February 1937

FIG. 9-B
Abscess of right psoas
July 1937

FIG. 9-C
Left femur
February 1937

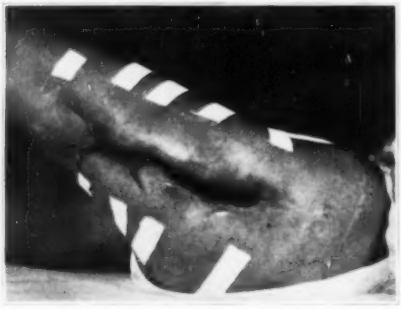

FIG. 9-D
Left femur
July 1937

Since the advent of streptomycin, combined with judicious surgery, we have been able to reverse our ideas with respect to the four dicta mentioned in this paper.

The following cases illustrate the application of these new principles.

CASE REPORTS

Group I: Unstabilized, Progressive

CASE 1. W. T., age five, was admitted in April 1947 (Fig. 1-A) with lesions of the second, third, and fourth thoracic vertebrae, complicated by a paravertebral abscess, pneumonitis, and an extrapulmonary abscess. The sedimentation rate was 40 millimeters per hour (Westergren). Surgical fusion was done in May 1948. The patient was discharged in December 1950 (Fig. 1-B).

CASE 2. B. P., age fifty-four, was admitted in October 1950 with lesions of the fifth and sixth thoracic vertebrae, complicated by a paravertebral abscess (Fig. 2-A). The sedimentation rate was 112 millimeters per hour (Westergren). Streptomycin therapy was begun and surgical fusion was performed in December 1950. In February 1951 (Fig. 2-B) the sedimentation rate was 26 millimeters.

CASE 3. D. M., age twenty-nine, was admitted in February 1949 with uncomplicated lesions of the second and third lumbar vertebrae (Fig. 3-A). The sedimentation rate was 90 millimeters per hour (Westergren). Streptomycin therapy was begun and surgical fusion was performed in May 1949. In December 1950 (Fig. 3-B) the sedimentation rate was 22 millimeters.

CASE 4. O. S., age twenty, was admitted in May 1948 with pulmonary tuberculosis. Tuberculous osteitis of the upper portion of the humerus with extension into the shoulder joint had developed in March 1948. Streptomycin therapy was begun and surgical excision and débridement of the local lesion in March 1949 were followed by secondary closure in one week. All wounds had healed in May 1949.

CASE 5. J. N., age forty-one, was admitted in June 1949 with osteitis of the greater trochanter and a local abscess. Streptomycin therapy was begun and surgical excision and débridement of the local lesion were performed in June 1949, followed by secondary closure at six weeks. The wound was healed in August 1949.

FIG. 10-A
Left buttock
March 1941

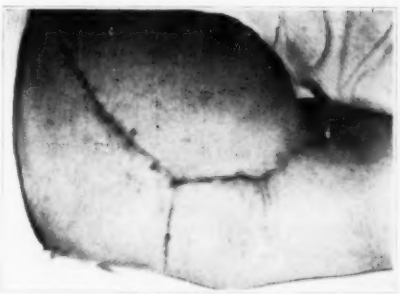

FIG. 10-B
Left buttock
March 1942

CASE 6. A. S., age forty-one, was admitted in May 1948 with osteitis of the left greater trochanter and a local abscess (Fig. 4-A). There was no streptomycin therapy. Surgical excision and débridement of the local lesion was performed in May 1948 followed by secondary closure in two weeks. The wound was healed in July 1948 (Fig. 4-B).

Group II: Multiple Lesions

CASE 7. V. M., age forty, was admitted in March 1947 with tuberculosis of the right shoulder joint (Fig. 5-A) complicated by old pulmonary, sacro-iliac, tarsal, and lumbar lesions. Streptomycin therapy was begun and surgical extirpation of the shoulder girdle was performed, with primary closure in April 1947. The wound was healed in September 1947.

FIG. 11
March 1951

CASE 8. C. S., age twenty-six, was admitted in November 1948 with pulmonary tuberculosis, and later lesions of the left fifth metatarsal bone (Fig. 6-A) and the right lateral malleolus (Fig. 6-C) developed. Streptomycin therapy was begun, and surgical excision of the fifth metatarsal with primary closure was performed in August 1949. The wound was healed in March 1950 (Fig. 6-B). Surgical excision of the lateral malleolus without opening the ankle joint was performed with primary closure in April 1950. The wound was healed in June 1950 (Fig. 6-D).

CASE 9. D. S., age twenty-two, was admitted in July 1949 with tuberculosis of the right elbow (Fig. 7-A), right knee (Fig. 7-C), and the fourth and fifth lumbar vertebrae (Fig. 7-E), complicated by pulmonary and renal tuberculosis. The sedimentation rate was 76 millimeters per hour (Westergren). Streptomycin therapy was begun and surgical excision (Ollier) of the right elbow was performed in November 1949. The wound was healed in February 1950. Resection of the right knee was done in December 1949. The wound was healed in June 1950. Fusion of the lumbar spine was carried out in June 1950. The patient was ambulatory in January 1951.

Group III: Surgery in the Presence of Abscesses, Sinuses, and Active Progression

CASE 10. J. B., age fifty-six, was admitted in May 1945 with extensive tuberculous tenosynovitis of the wrist. Excisions of the involved tissues attempted in 1946, 1947, and early in 1948 had failed; recurrence and abscess formation followed. Streptomycin therapy was begun and arthrodesis of the wrist was performed with débridement and primary closure in November 1948. The wound was healed in June 1949.

Case 11. M. A., age fifty-eight, was admitted in May 1945 with tuberculous sacro-iliac arthritis complicated by an iliac abscess and anterior and posterior sinuses. No streptomycin therapy was used until 1949. Excision of the sinuses, débridement of the abscess, and arthrodesis of the sacro-iliac joint were performed in May 1946. Excision of another sinus was carried out in November 1947. Another excision of a sinus was performed in January 1949, followed by secondary closure four weeks later. The wounds were healed in December 1949.

This case could also be classified in Group IV.

Case 12. F. K., age forty-two, was admitted in September 1942 with multiple lesions, including one of the acromioclavicular joints with local abscess and sinus. No streptomycin therapy was used. Surgical excision of the lesion was performed in February 1946, followed by secondary closure in one week. The wound was healed in April 1946.

Case 13. L. B., age twenty-one, was admitted in January 1951 with rapidly progressive pulmonary tuberculosis, a spinal abscess, and an open lesion of the fifth metacarpal bone (Fig. 8-A). Streptomycin therapy was begun and surgical excision of the metacarpal lesion was performed in February 1951 with primary closure. The wound was healed in March 1951 (Fig. 8-B).

Group IV: Extirpation by Excision of Extensive Abscesses and Sinuses

Case 14. D. B., age twenty, was admitted in January 1937 with a fused tuberculosis of the lumbar spine complicated by a large abscess of the right psoas (Fig. 9-A) which had been drained in October 1935, debrided in December 1936, and which was healed by September 1937. There was an extensive abscess on the left thigh (Fig. 9-C) which was excised in February 1937 and debrided again in March, April, June, and September 1937. The wounds were healed in December 1937.

Case 15. G. C., age twenty-seven, was admitted in October 1939 with pulmonary tuberculosis and sinuses of the left buttock and thigh (stump from amputation performed in 1937). No streptomycin therapy was employed. Surgical débridement was done in February 1941 and again in May and July 1941. Plastic revision was carried out in November 1941 with primary closure in December 1941. The wound was healed in March 1942 (Fig. 10-B).

Case 16. J. F., age fifty-four, was admitted in October 1944 with a lesion of the rib; despite resection in December 1944 an abscess developed which undermined the whole posterior trunk by March 1946. A complete subfascial débridement of the back was performed in March 1946, requiring thirty-eight inches of incision and débridement of 272 square inches. Secondary closure was carried out two weeks later. The wound was healed, except for a small debrided area, in November 1946. The patient became ambulatory, but later died (May 1947) of miliary tuberculosis of other origin.

Case 17. J. M., age twenty-two, was admitted in November 1947 with pulmonary tuberculosis and a thoracolumbar tuberculous lesion. Streptomycin therapy was begun and surgical fusion was performed in September 1948. Miliary tuberculosis and retinitis supervened in February 1949. A right peridural abscess was found in February 1949 and debrided in April 1949, followed by closure in May 1949. A left suberector spinal abscess developed in October 1949, which was debrided in November 1949, followed by secondary closure. The wound was healed in January 1950. An abscess developed on the right psoas in April 1950. This was debrided in September 1950, with partial secondary closure, and was healed in January 1951 (Fig. 11). An abscess on the right thigh developed in August 1950; this was debrided in October 1950 and was healed by January 1951. The patient has been ambulatory.

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1. Evans, E. T.: Compound Fractures and Osteomyelitis. Staff Bull. Hosp. Univ. Minnesota, **17:** 337–339, 1946.
2. Jury Review of Bone and Joint Cases. *In* Minutes of the Eighth Streptomycin Conference. Veterans Administration Area Office, Washington, D. C., 1949.

STREPTOMYCIN IN THE TREATMENT OF BONE AND JOINT TUBERCULOSIS *

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It has been more difficult to demonstrate the value of streptomycin in the treatment of bone tuberculosis than in the treatment of pulmonary lesions. This is due to the necessity of referring to the x-ray film as the final standard of comparison when assessing the progression or regression of a lesion. Roentgenograms of bone show changes much more slowly than do those of pulmonary disease, so that usually many months and sometimes years elapse before the roentgenographic appearance of a lesion can be said to show healing. If an abscess or draining sinus is present, its progress can often be used as an indication of the progress of the underlying bone lesion. Sometimes changes in lesions in the lungs or kidneys of a patient can be used to guess at progress in the bone lesion. Laboratory tests, such as the blood-sedimentation rate, may indicate whether tuberculous activity is waning or remains unaltered. Apart from these criteria, the only signs of the efficacy of streptomycin are clinical and far from exact.

Although we were fully aware of these limitations, an attempt is made in this paper to assess the results of streptomycin therapy in a group of 118 cases of bone and joint tuberculosis treated in 1947, 1948, 1949, and 1950 at the Toronto Hospital for Tuberculosis, Weston, Ontario. It was not planned in any case to use streptomycin as a definitive treatment, but only in conjunction with measures which have long been accepted as beneficial.

ADMINISTRATION AND DOSAGE OF STREPTOMYCIN

The usual form of administration was one-half gram of streptomycin given twice daily by intramuscular injection. In only two cases was a semiweekly administration used. Local injection into sinuses was rarely used, and then only when intramuscular administration had failed to bring about closure of the sinuses. In 1950 para-aminosalicylic acid was given concurrently in all cases except the few patients who could not tolerate the drug, the daily dose ranging from two grams to ten grams, the usual dose being ten grams divided into three doses. The total dosage of streptomycin most commonly used was sixty or ninety grams, but in a few cases 180 grams were given for special reasons. Included also are two patients treated in 1947 with total dosage of 350 and 360 grams. In the group of cases in which streptomycin was given to cover a surgical operation through a tuberculous field, a total dose of thirty grams was used unless the activity of the disease warranted larger doses. Although it was necessary, in a number of cases, to change over to dihydrostreptomycin because of vestibular or auditory disturbances, in only two of the 118 was it necessary to curtail the originally planned course of streptomycin. The only cases of permanent damage were: (1) three of the patients in the meningitis group became deaf; and (2) one patient, treated in 1947 with 360 grams of streptomycin, became ataxic.

CLASSIFICATION AND GROUPING OF CASES

For convenience of study, the entire group has been divided into the following four sub-groups:

* Read at the Annual Meeting of The American Orthopaedic Association, White Sulphur Springs, West Virginia, June 23, 1951.

A. *Streptomycin Combined with a Surgical Procedure* (Forty-two Patients)

This group of cases yielded more successful results than any other. It was perhaps to be expected that the high degree of success which, in pre-streptomycin days, attended careful excision of tuberculous foci and their sinuses would be enhanced by the addition of this antibiotic, and this expectation was fully justified by the results obtained. Only three of the forty-two patients failed to obtain healing which was both primary and permanent. In two of these failures, the chief cause was poor postoperative hemostasis, but the sinuses closed after draining for several weeks. In the third, an abscess was excised, but the focus of disease in the spine was inaccessible and was left behind, causing a recurrence of the abscess. Fortunately even this healed several months later. The results in this group are as follows:

	Cases	*Primary Healing*	*Delayed Healing*
1. *Operating through a Tuberculous Field*			
a. Excision of tuberculous tissue (no secondary infection)			
Abscess of spine (5), trochanter (2), pelvis (1), or chest wall (5)	13	12	1
Arthrodesis of knee joint	6	6	
Excision of sternoclavicular joint	1	1	
Tenosynovectomy	1	1	
b. Excision of tuberculous tissue (with history of recent secondary infection)			
Abscess and sinus from ischium, hip, and metacarpal (one each)	3	3	
Arthrodesis of knee joint	2	2	
c. Bone-grafting operations			
Hip (2), elbow (2), ankle (1), subtalar joint (1)	6	6	
Sacro-iliac	3	1	2
2. *Operating Adjacent to but outside a Tuberculous Field*			
Hip arthrodesis (complicated by renal and bone lesions)	5	5	
Spinal bone graft (complicated by pulmonary and renal lesions)	2	2	
Total	42	39	3

The use of streptomycin in this second group of seven cases was prophylactic rather than therapeutic, and primary healing was to be anticipated even had no antibiotic been available. These cases may be classified as substandard risks for surgery, due to the presence of more extensive or more destructive tuberculosis than the average case requiring arthrodesis, and this justifies the use of streptomycin.

B. *Streptomycin Alone for Persistently Draining Sinuses* (Thirty-two Patients)

In this group, streptomycin was used without the benefit of surgical excision of the tuberculous focus, usually because such an operation was very difficult or quite impossible, but sometimes because the patient's general condition did not warrant an operation. Streptomycin was given daily intramuscularly but not locally into the sinus except in three patients whose sinuses did not heal after the usual course of treatment. Following daily local treatment for three to four months in these three, the sinus closed permanently in one patient, closed for seven months in a second patient, and in the third patient remained open until excised surgically with its focus some time later. The daily dose of streptomycin injected into each sinus was 0.25 gram.

The eighteen sinuses which yielded hemolytic *Staphylococcus aureus*, as well as tubercle bacilli, were treated with penicillin, or sometimes with sulfadiazine or gantrisin if the organisms were sensitive to these agents. Usually this antistaphylococcus treatment was started first, and the streptomycin was added later if the sinus failed to heal promptly. In these cases, streptomycin alone is usually unable to bring about healing, and familiarity with all the antibacterial agents is necessary.

The fourteen uncontaminated tuberculous sinuses were treated by streptomycin alone except for one patient with bilateral mid-tarsal tuberculosis. This patient had previously taken, without obvious benefit, a course of 183 grams of streptomycin, including some injections into the abscesses before they broke down and formed sinuses. Later the lesions were treated by a course of 1420 grams of para-aminosalicylic acid in 142 days without streptomycin. Healing was obtained in two months, but on rare occasions thereafter one sinus reopened for a day.

The lesions treated were of fifteen spines, eight hips, two knees, two ribs, and one each of shoulder, elbow, trochanter, and foot. The final results in this group of thirty-two were good, but in some cases ultimate healing was achieved by adding surgery, penicillin, or sulfonamides to treatment by streptomycin. Only three sinuses remained unhealed, and one of these had been draining for fourteen years when streptomycin treatment was begun.

	Cases
1. *Uncontaminated Tuberculous Sinuses*	
a. Closed *permanently* during the first course of streptomycin	6
b. Closed *temporarily* during the first course of streptomycin but re-opened (three closed again spontaneously, a fourth during a second course of streptomycin, and a fifth after excision)	5
c. Failed to close at all during the first course of streptomycin (but one later closed following excision, one after local injection of streptomycin, and one spontaneously ten months after conclusion of streptomycin treatment)	3
2. *Secondarily Infected Tuberculous Sinuses*	
a. Closed *permanently* during first course of streptomycin (six also had penicillin; three had penicillin and sulfadiazine; one had streptomycin alone)	11
b. Closed *temporarily* during first course but re-opened. (One later closed under sulfadiazine; one closed during a second course of streptomycin and penicillin; one closed for seven months after local injections of streptomycin and then re-opened; one remains open despite a second course of streptomycin and penicillin and one of gantrisin)	4
c. Failed to close at all during first course (one closed spontaneously seven months later; one closed after two courses of penicillin, a course of sulfadiazine, and finally a course of gantrisin; the third is steadily improving, but the lesion has not yet closed)	3

Final Result: The lesions in twenty-nine of thirty-two cases are now healed (90 per cent.).

C. *Streptomycin for Tuberculosis of Bone, without Sinus Formation* (Thirty-four Patients)

No auxiliary surgical measures were employed in these cases.

It is in this group that assessment of the result is most difficult, because little or no roentgenographic change in the lesion can be seen, unless an abscess shadow is present and alters in size during treatment. Some of the cases were diagnosed in so early a stage that it was hoped that the usual course of the disease would be aborted by the action of streptomycin, but this was not often the case. New lesions sometimes appeared or abscesses grew larger, even during the course of treatment. On the other hand, a few lesions were aborted; one girl who had four early lesions in the spine and died from a non-tuberculous complication was found at post-mortem examination to have had no abscess associated with any of her spine lesions. This might be regarded as evidence in favor of the beneficial effect of streptomycin.

This group included twenty-five cases of tuberculosis of the spine, three of the knee, two of the hip, and two of the shoulder, one of the sacro-iliac joint, and one of the mid-tarsal joint. Of course, many in this group had multiple bone lesions, with or without pulmonary or renal tuberculosis. An attempt to classify the end result shows that in twenty healing was at least as good as, and probably quicker than, could have been expected without streptomycin. In fourteen, the result was certainly no better than what would have been classified as a slow or somewhat disappointing result in the pre-streptomycin days, although all but two have achieved sound healing or are well on their way to recovery. Each of these two continues to respond favorably to streptomycin when it is

given, but relapse occurs when it is withdrawn. Thus, of thirty-four cases, only two to date can be said to have an unfavorable prognosis. Perhaps this fact alone is good evidence in favor of the value of streptomycin.

Whether or not streptomycin can be expected to accelerate healing in closed tuberculosis of bones and joints is a matter of great importance, though controversial and hard to decide. Because of this, the erythrocyte sedimentation test was used in conjunction with clinical findings, in an attempt to reach conclusions which would pass critical scrutiny. Unfortunately, the sedimentation rate proved to be of uncertain value. During the course of streptomycin therapy, its behavior was as follows:

	Cases
A fall from pathological elevation to normal rate in	13
No significant change in	18
A rise from normal to a pathologically high rate in	1
Sedimentation rate during streptomycin therapy not known	2

Unfortunately the clinical progress did not always match the fluctuations in the sedimentation rate. For instance, no cause could be found for the rise in one case of spinal and renal tuberculosis during a course of 180 grams of dihydrostreptomycin and 900 grams of para-aminosalicylic acid in ninety days. His urine became negative for bacilli and his spine lesion remained quiescent, but his erythrocyte sedimentation rate rose from 6 to 33 during treatment, and three months later was 65. Nevertheless, clinically he had to be classified as showing very satisfactory improvement.

For clinical reasons the thirty-four patients were divided into two groups as follows:

1. *Definite and Sustained Improvement, Locally or Generally*

Spines		15	
Abscesses disappeared quicker than expected	5		
No abscesses formed from multiple lesions	1		
Spontaneous ankylosis of spine lesion	1		
Rapid control of spinal disease with prolonged apparent healing of renal tuberculosis	4		
Rapid control of spinal disease with complete healing of pulmonary tuberculosis	2		
Extensive spinal disease rapidly controlled	2		
Hip		1	
Subsidence of local and systemic symptoms	1		
Knees		2	
Rapid control and no relapse	2		
Shoulder		2	
Abscess disappeared and lesion healed	2		
Total			20 Cases

2. *Early Lesions not Aborted; Recovery Slow*

Spine		10	
Abscess became large or recurred	1		
New lesions developed	2		
Spine lesion appeared during streptomycin treatment for pulmonary tuberculosis	2		
Persistence of spine lesion and progression of pulmonary lesion	1		
Persistent pain and high sedimentation rate	1		
Hip		1	
Progressive destruction of bone starting from minimal lesion	1		
Knee		1	
Recurrence of synovitis after temporary disappearance	1		
Mid-tarsal joint		1	
Lesions progressed and new foci appeared	1		
Sacro-iliac joint		1	
Abscess formed. Epididymitis appeared	1		
Total			14 Cases

However, in this group of fourteen patients who did not seem to respond to streptomycin as well as expected, twelve ultimately became suitable for operations, such as spine fusion and arthrodesis of hip, sacro-iliac, or knee joints. Six have been discharged from

the hospital and have remained in good health. In only two cases is the ultimate prognosis uncertain.

D. *Streptomycin for Bone and Joint Lesions Complicated by Miliary Tuberculosis of Lungs, by Meningitis, or by Both* (Ten Patients)

The following cases suggest that the result in bone tuberculosis, if diagnosed early and associated only with demonstrable miliary tuberculosis of the lungs, is good, while in cases complicated by miliary and meningeal tuberculosis it is dubious or bad, due to the involvement of the meninges. The series is very small.

1. *Miliary Tuberculosis of Lungs Associated with the Following Five Joint Lesions:*

Synovitis of Knee: Both lesions disappeared 1

Tuberculosis of Hip: Pulmonary lesion disappeared
Bone lesion did not progress 2

Tuberculosis of Spine: Pulmonary lesion and epididymitis disappeared. Bone lesion did not progress and has been grafted 1

Double Tuberculous Lesion of Spine: Pulmonary lesion disappeared; empyema slowly subsided. Bone lesions were slowly controlled and finally grafted 1

All of these five patients have done well. Grafting has been done in the two with spine lesions. The tuberculous knee did not require arthrodesis and has recovered a full range of movement. Both of the hip-joint lesions are quiescent and appear cured. Roentgenographically, one shows no loss of bone or cartilage and has a nearly normal range of movement. In the second case the disease progressed to some destruction of the acetabulum and the femoral head, but under streptomycin therapy there has been progressive reconstruction of the bone (Figs. 1-C and 1-D). This patient is now walking without pain and has one-quarter of the normal range of hip-joint movement.

2. *Miliary Tuberculosis and Tuberculous Meningitis Associated with the Following Two Spine Lesions:*

Tuberculosis of Spine: Pulmonary lesion improved; spine lesion remained unchanged; and epididymitis appeared.
Meningitis was cured after two years with residual headaches intermittently 1

Tuberculosis of Spine: Pulmonary lesion cleared; renal lesion appeared.
Meningitis disappeared, but recurred and was fatal. 1

3. *Tuberculous Meningitis and the Following Three Joint Lesions:*

Tuberculosis of Spine: Fatal while still under streptomycin treatment 1

Tuberculosis of Spine: Multiple bone lesions and sinuses healed. Pulmonary lesion static.
Meningitis disappeared, but recurred with schizophrenia and was fatal 1

Tuberculosis of Hip: Bone lesions improved. Meningitis disappeared but recurred and was fatal 1

None of these five patients did well, although one was cured of meningitis and is living today. In the most unusual case the patient had many bone lesions and was so thin that intramuscular streptomycin could not be used. She was given intrathecal streptomycin as a gesture three times a week so that in five and one-half months the total received was 11.5 grams. Blood levels varying from 2.5 to 20 micrograms per cubic centimeter were obtained, and all her sinuses healed. One month after cessation of streptomycin, her meningitis returned.

STREPTOMYCIN-SENSITIVITY TESTS

Definition of Sensitivity

All sensitivity tests were carried out on a solid medium (modified Herrold's) containing dilutions of streptomycin ranging from 0 to 0.5 micrograms per cubic centimeter to 2.0, 5.0, 10.0, 25.0, and 50.0 micrograms. If growth of the tubercle bacilli was inhibited by 10.0 micrograms or less, the organism was regarded as sensitive to streptomycin. Actually the clinical results obtained suggest that this is a reasonable definition. However, streptomycin was not withheld from any patient who needed it, even if he was known to be carrying resistant bacilli; and there appeared to be definite benefit from its use in some of these cases.

Results of Sensitivity Tests

Tests were initiated on every lesion from which tubercle bacilli could be recovered at the time of treatment. Occasionally this meant having recourse to an older culture on file in the laboratory, because the patient's pus had become negative for tubercle bacilli at the time streptomycin treatment was instituted.

Group I: No tubercle bacilli available during or after streptomycin therapy. When no culture was available, no tests could be carried out unless the patient had some other tuberculous focus which yielded bacilli. There were thirty-nine such patients of 118 (33 per cent.).

Group II: No bacilli available after streptomycin treatment. Of course in many patients the bacilli became resistant during streptomycin treatment, so that it was impossible to test for resistant forms at the termination of treatment. If any of these patients did harbor resistant bacilli, the clinical outcome did not appear to be impaired as most of the lesions ended by healing. There were forty-one of these patients with "converted" lesions, representing 34.7 per cent. of the entire group. In five of these patients, the bacilli were resistant as the result of previous sanatorium treatment, and yet the bacilli disappeared during streptomycin treatment.

Group III: Bacilli available during and after streptomycin treatment. There were thirty-six patients (30.5 per cent.) in whom tubercle bacilli were obtained for sensitivity tests both before and after a course of streptomycin therapy, and of these twenty-six remained sensitive throughout the course, five were sensitive before, but acquired resistance during treatment, and five were resistant both before and after treatment. These ten patients with resistant bacilli were distributed evenly among the four groups receiving streptomycin, as classified earlier in this paper.

(The other two patients included one whose tests have not yet been completed, and one who was treated by para-aminosalicylic acid alone, having at some previous time had a course of streptomycin therapy.)

Streptomycin Resistance

Since the adoption in 1950 of para-aminosalicylic acid treatment concurrent with streptomycin, resistance to streptomycin has not developed in any patient if the dose of para-aminosalicylic acid was ten grams daily. All but one of the fifteen patients reported in this series as being resistant acquired resistance in 1948 or 1949 when taking streptomycin without para-aminosalicylic acid. The one exception was in a patient given only two grams of para-aminosalicylic acid daily with streptomycin. Subsequent use of para-aminosalicylic acid did not reduce the degree of resistance in any of these cases. In this resistant group were five patients whose cultures became negative for bacilli during streptomycin treatment; they progressed well. There were five who yielded resistant forms of bacilli throughout treatment; but only one, who had meningitis, did badly, and three have been discharged in good health, with arrested lesions, after longer treatment than usual. There were five who had sensitive bacilli at the commencement of treatment, but showed resistant forms later, and they all did reasonably well, though perhaps they were slower than average in mastering their infection. It is worthy of note that, if emergence of resistant forms of bacilli is to be delayed by the use of para-aminosalicylic acid, ten grams or more daily should be used. Although only one patient in this orthopaedic series acquired resistance on two grams of para-aminosalicylic acid daily, a survey of all cases throughout the Hospital has indicated that a two-gram dose gives no protection.

SUMMARY AND DISCUSSION

The effect of streptomycin, one gram daily, with and without para-aminosalicylic acid, ten grams daily, in the course of treating 118 tuberculous lesions of bones and joints in 1947, 1948, 1949, and 1950 has been assessed.

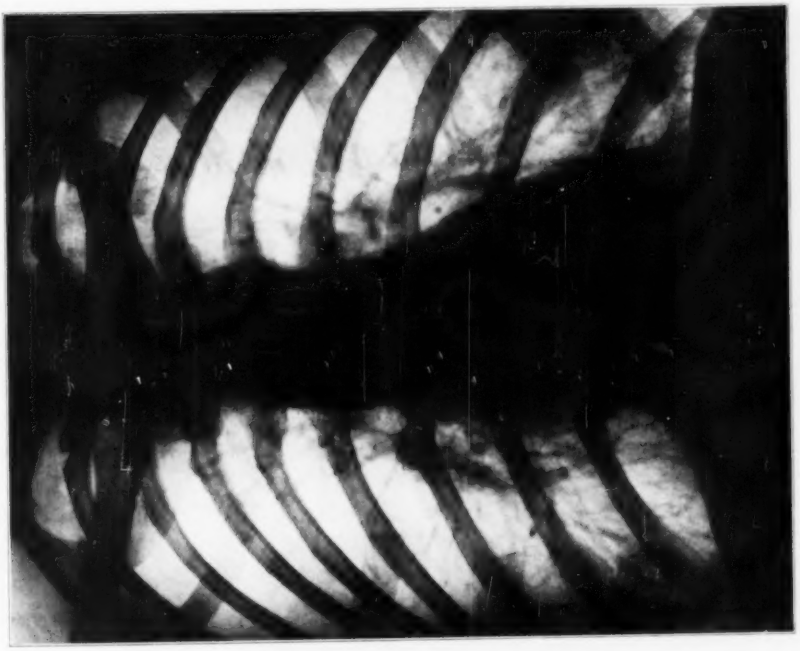

FIG. 1-B

FIG. 1-A

FIG. 1-C

FIG. 1-D

Effect of Streptomycin on Miliary Tuberculosis of Lung and Tuberculosis of Left Hip.
Female, age twenty-three on admission in June, 1950. Diagnosis: miliary tuberculosis of lung with active tuberculosis of left hip. Treatment: streptomycin, one gram, and para-aminosalicylic acid, ten grams, daily for six months. Result: cure of pulmonary miliary lesion and apparent cure of tuberculosis of the hip. Patient is walking without pain or muscle spasm and with a range of movement about one-quarter of normal.
Fig. 1-A: Chest on admission, June 1950. Fig. 1-B: Chest on discharge, December 1951.
Fig. 1-C: Left hip on admission, June 1950. Fig. 1-D: Left hip on discharge, December 1951.

The courses have varied from a total of as little as thirty grams to cover a surgical operation, to as much as 360 grams in the early days of streptomycin therapy, when three grams a day was used. The most common doses were sixty grams and ninety grams. The cases have been grouped according to the indications for streptomycin rather than to the dosage used.

The best results were obtained when streptomycin treatment was associated with excision of a tuberculous focus. In some instances pyogenic infection had previously been present and controlled by the use of suitable antibacterial agents. Of thirty-five operations through a tuberculous field, primary healing was obtained in thirty-two and delayed healing in three. There were no complete failures.

When persistent tuberculous sinuses from bone were treated by streptomycin, but not by excision, the results were nearly as good, but slower in appearing. Of fourteen uncontaminated sinuses, only six closed permanently during treatment; but five more closed after one recurrence, with or without more streptomycin; two closed after excision; and one closed spontaneously ten months after termination of streptomycin therapy. When the added factor of pyogenic bacteria had been faced in eighteen cases, additional antibiotics were required, but the results were about the same. There were eleven permanent closures during treatment, four subsequent closures following one recurrence, and three partial failures. Some of these sinuses, so difficult to close, had been draining for between fourteen and twenty-three years, but twenty-nine out of thirty-two (90 per cent.) are now healed. Only one of these appears to be too great a problem to permit a good prognosis to be made.

In the treatment of non-discharging bone lesions, the results attributable to streptomycin in thirty-four cases appeared to be good in twenty cases (59 per cent.) and disappointing in fourteen cases (41 per cent.), when judged by clinical and roentgenographic findings. This group is difficult to assess because of the slowness with which objective evidence of healing can be obtained and because the long-term results from standard treatment alone were very good, even before the advent of streptomycin.

When bone and joint lesions were complicated by miliary tuberculosis of the lungs (five cases), treatment was modified by increasing the course of streptomycin to 180 grams spread over six months or more, as well as by the use of intrathecal injections. The results were excellent, as the pulmonary lesions completely disappeared and it was possible ultimately to bone-graft two spine lesions. Two hip lesions appear to have been arrested, one with no bone destruction. One synovial lesion of the knee has been aborted. The surprising results obtained in the three cases last mentioned may indicate that *early* treatment of bone lesions with adequate doses of streptomycin and para-aminosalicylic acid for a *prolonged* period of time offers real hope of cure of tuberculosis of bones and joints. In these cases the miliary tuberculosis of the lung necessitated prolonged administration of streptomycin and para-aminosalicylic acid. The patient with a tuberculous knee received 129 grams of streptomycin and 2,290 grams of para-aminosalicylic acid over seven and one-half months; one patient with a hip lesion, 180 grams of streptomycin and 360 grams of para-aminosalicylic acid over six months. There was no destruction of the joint in this case. The second patient with a tuberculous hip received 180 grams of streptomycin and 640 grams of para-aminosalicylic acid over six months, followed by a further course of 2,025 grams of para-aminosalicylic acid over the following four and one-half months. The roentgenograms of this patient are reproduced in Figures 1-A and 1-B.

When tuberculosis of bone was complicated by meningitis, the results were temporarily encouraging but ultimately poor. Only one patient out of five has survived, but he has lived for two and one-half years since the onset of miliary tuberculosis and meningitis.

Sensitivity tests were carried out on all lesions with tubercle bacilli, using modified Herrold's medium. No bacilli were available in 33.0 per cent., the lesions became non-bacillary during treatment in 34.7, and final determinations of sensitivity have been made in only 30.5 per cent. Of this last group, 72 per cent. yielded bacilli sensitive to streptomycin throughout treatment, fourteen per cent. gave bacilli which became resistant, and fourteen per cent. started with resistant bacilli and continued to yield them throughout treatment. Resistant forms of bacilli did not emerge in any patient treated concurrently with both streptomycin and para-aminosalicylic acid, provided the tubercle bacilli were sensitive to begin with, that para-aminosalicylic acid was used from the commencement of streptomycin treatment, and that the dose of para-aminosalicylic acid was not less than ten grams daily.

Response to streptomycin was perhaps impaired to some degree in the patients who harbored resistant forms of tubercle bacilli. However, the only group of patients who have done badly is the group with meningitis, and among the remaining 113 patients there have been only two deaths, one from cerebral embolism and one from a ruptured aneurysm. The prognosis in the least promising of the other 111 is reasonably good.

There is no doubt that the use of streptomycin and para-aminosalicylic acid has reduced morbidity and increased the prospects of successful treatment in the field of bone and joint tuberculosis. It is of the greatest value in promoting primary healing of a closed wound after excision of a tuberculous sinus and its focus of origin.

EVALUATION OF STREPTOMYCIN THERAPY IN A CONTROLLED SERIES OF NINETY CASES OF SKELETAL TUBERCULOSIS

A Public Health Service Cooperative Investigation *

Late in 1947, the Tuberculosis Study Section of the Division of Research Grants of the National Institutes of Health initiated a series of centrally coordinated investigations, in which a number of physicians at various medical centers participated, to evaluate the effect of streptomycin in the treatment of tuberculosis.

One portion of this program, the Skeletal Control Study, encompasses a broad range of bone and joint tuberculosis, excluding only those patients for whom there might be a life expectancy of less than one year without streptomycin. The patients were divided into two groups by a random method, with the use of streptomycin restricted to one group.

The five participating investigators are:

Dr. Edward L. Compere, Children's Memorial Hospital, Chicago, Illinois

Dr. Samuel Kleinberg and Dr. Barnard Kleiger, Hospital for Joint Diseases, New York, N. Y.

Dr. Philip H. Moore, Mt. Edgecumbe Hospital, Mt. Edgecumbe, Alaska

Dr. Marcus J. Stewart, Campbell Clinic, Memphis, Tennessee

Dr. Peter B. Wright, Medical College of Georgia, Augusta, Georgia

The study was planned and coordinated by the Field Research Branch of the Division of Chronic Disease and Tuberculosis, United States Public Health Service, under the direction of Mrs. Shirley H. Ferebee. The report was prepared for the investigative group by Dr. Francis J. Murray, Mrs. Laura F. Rosen, and Norman Braunstein, who represented the United States Public Health Service in the medical and statistical coordination of the study. The opinions expressed in this report represent the consensus of the investigators.

Between April 1948 and April 1950, 108 patients came under study. The present paper reports on an evaluation of ninety cases which have been observed for fifteen months. Eighteen cases were not evaluated because of technical deficiencies in the data.†

The forty control and fifty streptomycin cases were evaluated according to objective criteria by an Evaluation Panel composed of Dr. Ralph K. Ghormley, of the Mayo Foundation, Dr. Edward T. Evans, of the University of Minnesota, and Dr. William H. Bickel, of the Mayo Foundation. While the number of cases is much too small to permit definite conclusions, and the chance variation in the results is obviously large, the differences and the nature of the differences between the two groups give at least an indication of the effect of streptomycin in the treatment of skeletal tuberculosis.

MATERIALS AND METHODS

A few pertinent points on the selection, management, and observation of cases included in the study should be mentioned:

First, each investigator proposed those cases under his care which he felt were suitable for the control study. The materials on these patients were reviewed by Dr. Edward L. Compere, Selection Chairman, who determined whether or not each case met the established criteria for suitability for this study. Suitability was based primarily on roentgeno-

* A study of fifty patients was originally presented by Dr. Philip H. Moore at the Sixty-fourth Annual Meeting of The American Orthopaedic Association, at White Sulphur Springs, West Virginia, June 23, 1951. Subsequently the report was revised to include findings for ninety patients.

† No film at date of admission to study 12
No information received after admission to study 2
Subsequent diagnosis non-tuberculous (at hospital) 2
Streptomycin given in control case in error 2

graphic evidence of a tuberculous process of the bone or joint or of both, together with bacteriological confirmation from sinus drainage, abscess aspiration, or biopsy specimen; microscopic demonstration of the tuberculous nature of the lesion on biopsy, and general corroborative evidence from the clinical picture. The accepted cases were allocated to the streptomycin or control group by a random method in a central office, the Division of Chronic Disease and Tuberculosis of the United States Public Health Service.

Second, uniform clinical and laboratory observations and roentgenograms were made by all investigators and were reported to the central office at three-month intervals.

Third, the only variable in the management of the two groups was streptomycin; all other forms of treatment or surgery being available to both groups. Patients in the streptomycin group received a daily intramuscular dose of twenty milligrams of streptomycin per kilogram of body weight for ninety-one days. Longer drug therapy was allowed if considered advisable by the investigator, and ten patients in the streptomycin group received more than one course.

Fourth, control patients received no streptomycin for fifteen months with the exception of one patient in whom meningeal tuberculosis developed, and of three in whom developed other tuberculous complications considered by the Appeals Board "life-threatening and potentially amenable only to streptomycin".

Because of the decline in the prevalence of bone and joint tuberculosis in the continental United States, fewer cases than were anticipated have been available for study from the four participating clinical centers in the United States proper, and more than one-half of the cases in the study are from Alaska. Eighty-seven per cent. of the patients evaluated were less than twenty years of age when admitted to the study. The primary focus was the spine in 50 per cent., the hip in 24 per cent., and in the remaining 26 per cent. it was distributed among a number of other locations. In a large majority of the cases, the skeletal involvement was extensive and the lesions progressive.

The composition of the group of forty control and fifty streptomycin patients has been examined with respect to age, race, and sex, antecedent duration of disease, length of previous hospitalization, subjection to fusion procedures, dysfunction, temperature, sedimentation rate, and hemoglobin levels at time of admission to study. Only small differences existed between the two groups. A detailed comparison of the two groups at the time of selection for study is found in Tables V and VI. The similarity of the two groups at the beginning of observation, obtained by chance allocation of cases to the streptomycin and control groups, justifies the assumption that changes appearing later are due to the variable under investigation, streptomycin therapy.

RESULTS

The results of treatment during fifteen months of observation have been measured in terms of the judgments made on each case by the Evaluation Panel, and of the clinical observations reported by the investigators.

The method in which the Panel functioned may be briefly explained. Each panel member worked independently, without knowing the judgments of the other two members and without knowing the allocation group of the case under consideration. For each case, he made a series of judgments as to initial status and change from x-ray films alone. Then, on the basis of the films and abstracts of the reported clinical data, he made a second series of judgments on the combined material.

Data are presented in terms of the opinion of the majority. Although opinions with regard to change were expressed separately for each focus when a patient had multiple skeletal lesions, the findings for secondary and tertiary foci agreed so closely with those for the primary lesion that data are reported in terms of patients rather than in terms of lesions.

One streptomycin and one control patient died in the course of study. Three other patients originally allocated to the control group were allowed recourse to streptomycin

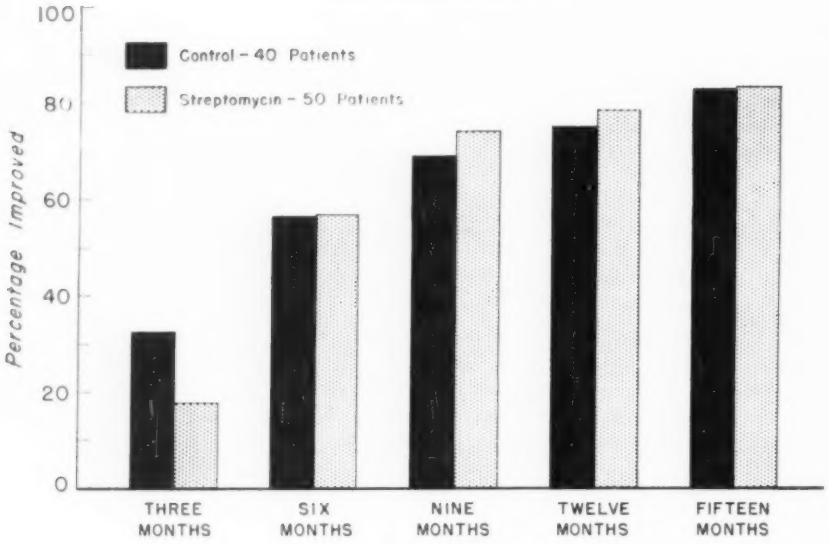

CHART I

Percentage of skeletal tuberculosis patients in control and streptomycin groups with roentgenographic evidence of improvement at three, six, nine, twelve, and fifteen months.

before the end of the fifteen-month observation period. The latter are designated "appeal" cases and in the discussion which follows are grouped with those who did not improve.

TABLE I

NUMBER AND PERCENTAGE OF SKELETAL TUBERCULOSIS PATIENTS IN CONTROL AND STREPTOMYCIN GROUPS WITH X-RAY EVIDENCE OF IMPROVEMENT AT THREE, SIX, NINE, TWELVE, AND FIFTEEN MONTHS

	Cumulative Change from Time of Selection to:				
	3 months	6 months	9 months	12 months	15 months
	Number of Patients				
Control group					
Total	*40*	*40*	*40*	*40*	*40*
Improved	10	18	22	24	29
Unimproved	21	14	10	8	6
Not available	9	8	8	8	5
Streptomycin group					
Total	*50*	*50*	*50*	*50*	*50*
Improved	6	21	26	29	35
Unimproved	28	16	9	8	7
Not available	16	13	15	13	8
	Percentage of Patients *				
Control group					
Total	*100 0*	*100 0*	*100 0*	*100 0*	*100 0*
Improved	32 3	56 3	68 8	75 0	82 9
Unimproved	67 7	43 8	31 3	25 0	17 1
Streptomycin group					
Total	*100 0*	*100 0*	*100 0*	*100 0*	*100 0*
Improved	17 7	56 8	74 3	78 4	83 3
Unimproved	82 3	43 2	25 7	21 6	16 7

* Based on available opinions

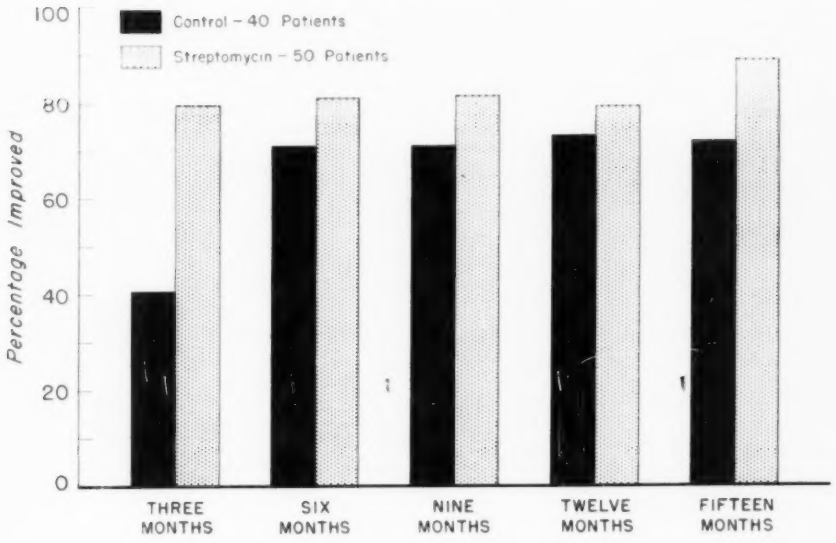

CHART II

Percentage of skeletal tuberculosis patients in control and streptomycin groups showing over-all improvement at three, six, nine, twelve, and fifteen months.

Change Judged by X-Ray Evidence Alone

Chart I and Table I show the proportion of each group with x-ray evidence of improvement at three, six, nine, twelve, and fifteen months after admission to the study. In the control group, 32 per cent. showed improvement after three months of observation, 56 per cent. at six months, 69 per cent. at nine months, 75 per cent. at twelve months, and 83 per cent. at fifteen months. In the streptomycin group, the percentages were 18, 57, 74, 78, and 83 at each successive observation point. The proportions are very much the same for the two groups. In both, there is a noticeable increase in the proportion of those who improved in between three and six months, and the improvement is even greater at fifteen months. These results may be summarized by saying that on the basis of x-ray evidence alone, the condition of the streptomycin group is essentially the same as that of the control group, and that more than four-fifths of the patients in both groups showed x-ray evidence of improvement by the end of fifteen months.

Change Judged by X-Ray and Clinical Evidence

After the Evaluation Panel had assessed the extent of change in each case detectable by x-ray alone, clinical and laboratory findings were added to the material available to the Panel in assessing changes occurring at three-month intervals in the patient's over-all condition. Although x-ray evidence alone failed to reveal significant differences between the control and streptomycin groups, Chart II and Table II show that, on the basis of the total evidence available, the jurors found a definite superiority among the streptomycin patients. These judgments were, like those on x-ray evidence alone, made without knowledge of the streptomycin or control status of any case.

Judged on the basis of the patient's total condition, 41 per cent. of the controls were improved at three months, 71 per cent. at six months, 71 per cent. at nine months, 73 per cent. at twelve months, and 72 per cent. at fifteen months. Among the streptomycin-

TABLE II

NUMBER AND PERCENTAGE OF SKELETAL TUBERCULOSIS PATIENTS IN CONTROL AND STREPTOMYCIN GROUPS SHOWING OVER-ALL IMPROVEMENT AT THREE, SIX, NINE, TWELVE, AND FIFTEEN MONTHS

	Cumulative Change from Time of Selection to:				
	3 months	6 months	9 months	12 months	15 months
	Number of Patients				
Control group					
Total	*40*	*40*	*40*	*40*	*40*
Improved	15	27	27	27	28
Unimproved	22	11	11	10	11
Not available	3	2	2	3	1
Streptomycin group					
Total	*50*	*50*	*50*	*50*	*50*
Improved	38	38	35	34	41
Unimproved	10	9	8	9	5
Not available	2	3	7	7	4
	Percentage of Patients *				
Control group					
Total	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*
Improved	40.5	71.0	71.0	73.0	71.8
Unimproved	59.5	29.0	29.0	27.0	28.2
Streptomycin group					
Total	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*
Improved	79.2	80.9	81.4	79.1	89.1
Unimproved	20.8	19.1	18.6	20.9	10.9

* Based on available opinions.

treated patients, improvement appeared in 79 per cent. at three months, 81 per cent. at six months, 81 per cent. at nine months, 79 per cent. at twelve months, and 89 per cent. at fifteen months. The streptomycin group was clearly superior at each point of observation. The greatest difference appeared at three months, when twice as many streptomycin patients as controls had improved, and an advantage was maintained throughout the period of observation. Even at the end of fifteen months, the controls had not reached the three-month level of the streptomycin group.

The difference between roentgenographic and over-all comparisons has interesting implications. The action of streptomycin appears to produce a generalized effect upon the patient's well-being and upon the secondary manifestations of the tuberculous process rather than a specific effect upon the local lesion. This effect on the secondary manifestations of the disease is perhaps best illustrated by the rather prompt cessation of sinus drainage, reduction in the sedimentation rate, the return toward a normal hemoglobin level, and finally evidence of greater improvement in functional ability.

After fifteen months of observation, the elevation of sedimentation rate present at the onset of study had been reduced to a clinically significant extent in 44 per cent. of the streptomycin patients but in only 14 per cent. of the control patients. At that time, improvement in hemoglobin values was reported for 50 per cent. of the drug group and for only 27 per cent. of the controls.

In Table III, the frequency of draining sinuses in the two groups at admission has been correlated with their frequency at fifteen months. Among patients with sinuses draining on admission, drainage still persisted at fifteen months or at time of appeal or death for four of the twelve observed in the control group and for one of the twelve in the streptomycin group. Of the remaining twenty-eight control and thirty-eight streptomycin patients without draining sinuses at admission, a sinus which continued to drain at fifteen months had developed in only one among the streptomycin group but sinuses had developed in four among the controls. Thus streptomycin apparently promoted

TABLE III

DISTRIBUTION OF SKELETAL TUBERCULOSIS PATIENTS IN CONTROL AND STREPTOMYCIN GROUPS, BY SINUS DRAINAGE AT ADMISSION TO STUDY AND AT FIFTEEN MONTHS

Sinus at 15 Months	Sinus at Admission to Study: Total	Drainage	No Drainage
	Number of Patients		
Control group			
Total	*40*	*12*	*28*
Drainage	5	1	4
Drainage at death or appeal	3	3	0
No drainage	30	7	23
No drainage at appeal	1	0	1
Indeterminate	1	1	0
Streptomycin group			
Total	*50*	*12*	*38*
Drainage	2	1	1
No drainage	46	10	36
No drainage at death	1	0	1
Indeterminate	1	1	0
	Percentage of Patients		
Control group			
Total	*100.0*	*100.0*	*100.0*
Drainage	12.8	9.1	14.3
Drainage at death or appeal	7.7	27.3	0.0
No drainage	76.9	63.6	82.1
No drainage at appeal	2.6	0.0	3.6
Streptomycin group			
Total	*100.0*	*100.0*	*100.0*
Drainage	4.1	9.1	2.6
No drainage	93.9	90.9	94.7
No drainage at death	2.0	0.0	2.6

healing and limited formation of new sinuses as shown by the fact that 21 per cent. of the control but only 4 per cent. of the streptomycin patients had drainage at time of appeal, at fifteen months, or at death.

The functional ability exhibited at fifteen months by patients in the two groups was evaluated on the following basis:

Excellent: Maximum function possible; no appliances worn; no restriction of activities.

Fairly good: Some functional impairment. Patient may or may not require appliance and restriction of activity.

Poor: Patient either requires complete bed rest with some type of appliance, or his functional end result reveals marked impairment. (This category includes cases of amputation, appeal, and death prior to fifteen months.)

TABLE IV

DISTRIBUTION OF SKELETAL TUBERCULOSIS PATIENTS IN CONTROL AND STREPTOMYCIN GROUPS, BY TIME OF SURGERY

Time of Surgery	Number of Patients: Control	Streptomycin	Percentage of Patients: Control	Streptomycin
Total	*40*	*50*	*100.0*	*100.0*
Prior to study	9	12	22.5	24.0
During 15 months of study	16	16	40.0	32.0
No surgery	15	22	37.5	44.0

TABLE V

CHARACTERISTICS OF SKELETAL TUBERCULOSIS PATIENTS IN CONTROL AND STREPTOMYCIN GROUPS AT ADMISSION TO STUDY

	Number of Patients		Percentage of Patients *	
	Control	Streptomycin	Control	Streptomycin
Total	*40*	*50*	*100.0*	*100.0*
Location of primary focus				
Spine	19	26	47.5	52.0
Hip	10	12	25.0	24.0
Other	11	12	27.5	24.0
Number of skeletal foci				
One only	33	44	82.5	88.0
More than one	7	6	17.5	12.0
Age (years)				
9 and under	25	27	62.5	54.0
10–19	10	16	25.0	32.0
20 and over	5	7	12.5	14.0
Sex				
Male	21	30	52.5	60.0
Female	19	20	47.5	40.0
Race				
White	7	9	17.5	18.0
Negro	11	9	27.5	18.0
Alaskan	21	28	52.5	56.0
Other	1	4	2.5	8.0
Duration of illness (months)				
0–24	12	14	30.8	28.0
25–48	13	17	33.3	34.0
49–72	7	9	17.9	18.0
73 and over	7	10	17.9	20.0
Not available	1	0		
Length of hospitalization (months)				
0–12	21	25	55.3	53.2
13–24	12	11	31.6	23.4
25 and over	5	11	13.1	23.4
Not available	2	3		
Previous streptomycin therapy				
Streptomycin	6	4	15.0	8.0
No streptomycin	34	46	85.0	92.0
Dysfunction				
Marked	17	19	47.2	41.3
Moderate	6	14	16.7	30.4
Slight	5	4	13.9	8.7
Fused	7	7	19.4	15.2
None	1	2	2.8	4.3
Not available	4	4		
Fusion				
None prior to study	31	38	77.5	76.0
Prior to study	9	12	22.5	24.0
Sinus				
No drainage	28	38	70.0	76.0
Some drainage	12	12	30.0	24.0
Temperature				
Normal	6	18	15.0	36.0
Occasional elevation	17	11	42.5	22.0
Mild, consistent elevation	17	21	42.5	42.0
Sedimentation rate				
Normal	6	9	15.0	18.0
Somewhat elevated	5	9	12.5	18.0
Moderately elevated	29	32	72.5	64.0
Hemoglobin				
Normal	5	4	12.5	8.0
Slightly subnormal	12	20	30.0	40.0
Moderately subnormal	23	26	57.5	52.0
Non-protein nitrogen or blood urea nitrogen				
Normal	40	50	100.0	100.0
Elevated	0	0	0.0	0.0

* Based on available opinions.

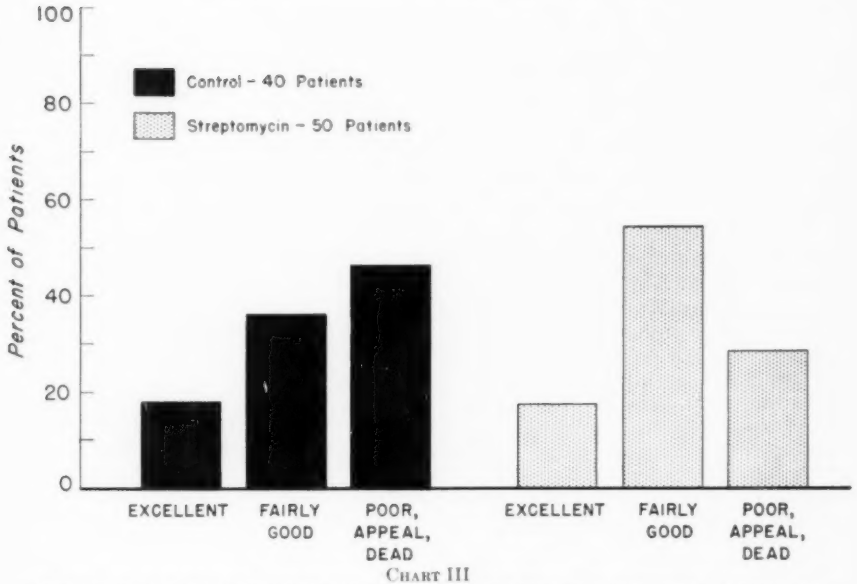

CHART III

Distribution of skeletal tuberculosis patients in control and streptomycin groups by ability to function at fifteen months.

At fifteen months, approximately 17 per cent. of the patients in each group had excellent ability to function; 54 per cent. of the streptomycin and 36 per cent. of the control group had fairly good functional ability, and 28 per cent. of the streptomycin and 46 per cent. of the control patients had only poor functional ability, had been appealed, or were dead. This is shown on Chart III.

Fusion

It is probable that much of the improvement noted reflects the effect of the performance of surgery. By fifteen months of study 63 per cent. of control patients and 56 per cent. of streptomycin patients had undergone surgery at some time during the history of their bone and joint tuberculosis. This is illustrated in Table IV, which shows the proportions receiving surgery before and during the study.

The panel members elected to evaluate fusion in terms of the extent of the intra-articular bony fusion actually achieved rather than in terms of the performance of surgery, which only initiates the fusion process. While solid bony fusion was seldom apparent as early as fifteen months, the Panel detected some x-ray evidence of bony fusion for 76 per cent. of control and 63 per cent. of streptomycin patients who had undergone surgery.

For the sixteen control patients who underwent surgery during this study, the average period from onset of bone and joint tuberculosis to surgery was forty-seven months; for the sixteen streptomycin patients, the average period was thirty-six months. With some few exceptions, surgery was confined to lesions of the hip and spine.

Of the fifteen control patients who had not undergone surgery, nine had improved at fifteen months, two were too ill for surgery, three were appealed, and one had contracted meningitis and died. Of the twenty-two streptomycin patients who had no surgery during the first fifteen months of study, fourteen made good progress without operation, five were operated upon after fifteen months, and one did not report after the third month. The investigator had contemplated surgery on the remaining two patients, but their condition was too poor to warrant surgery.

TABLE VI

INITIAL STATUS OF SKELETAL TUBERCULOSIS PATIENTS IN CONTROL AND STREPTOMYCIN GROUPS AS JUDGED FROM X-RAYS

	Number of Patients		Percentage of Patients *	
	Control	Streptomycin	Control	Streptomycin
Total	*50*	*50*	*100.0*	*100.0*
Degree of skeletal involvement				
Slight	1	5	2.6	10.0
Moderate	5	9	12.8	18.0
Extensive	33	36	84.6	72.0
Not available	1	0		
Bone collapse				
None	0	6	0.0	12.0
Slight	6	4	15.4	8.0
Partial	18	17	46.2	34.0
Complete	15	23	38.5	46.0
Not available	1	0		
Bone destruction				
Slight	3	5	7.7	10.0
Moderate	8	11	20.5	22.0
Marked	28	34	71.8	68.0
Not available	1	0		
Narrowing of joint space				
None	3	4	7.5	8.0
Slight	0	5	0.0	10.0
Moderate	5	4	12.5	8.0
Marked	32	37	80.0	74.0
Decalcification				
None	1	2	2.5	4.1
Slight	11	19	27.5	38.8
Moderate	26	20	65.0	40.8
Marked	2	8	5.0	16.3
Not available	0	1		
Sequestration				
Absent	25	29	62.5	59.2
Present	15	20	37.5	40.8
Not available	0	1		
Cold abscess				
Absent	17	22	43.6	45.8
Present	22	26	56.4	54.2
Not available	1	2		
Stage of skeletal lesion				
Improving	3	2	8.6	4.7
Quiescent	4	3	11.4	7.0
Deteriorating	28	38	80.0	88.3
Not available	5	7		

* Based on available opinions.

Thus it can be said that at fifteen months of study, or shortly thereafter, all streptomycin patients except two (both with lesions of the spine) whose improvement was dependent on surgery had undergone an operation. In contrast, six control patients (three with spine lesions and two with hip lesions, and one with involvement of the knee) for whom surgery was necessary had not been operated upon because of severity of illness.

DISCUSSION

In skeletal tuberculosis, as in all forms of illness, certain factors indicate a more favorable prognosis than others, quite apart from the form of therapy under consider-

ation. When improvement during observation is examined in terms of the characteristics of the total case material, certain generalizations covering both the streptomycin and control groups may be made. In general, improvement occurred more frequently among patients aged ten to nineteen than among either older or younger patients; among patients with moderate osseous involvement than among those with extensive involvement; among patients without cold abscess development or sequestration. Roentgenographic improvement was also more frequent among patients who had been hospitalized for more than one year at time of admission to study than among those who had been hospitalized a shorter period.

The data appear to substantiate the thesis that, because of the relative avascularity of bone lesions and because a tuberculous focus is usually isolated by fibrous-tissue walls, little streptomycin reaches the skeletal lesion. Hence the roentgenographic impression of progress is quite similar for the streptomycin and control groups. However, streptomycin may ameliorate the toxic effects of the tubercle bacillus and, in contiguous areas where the vascular supply is better, may stem the spread of the disease process and bring about systemic improvement. Clinically the streptomycin patient is in better condition than the control patient at all points of observation.*

CONCLUSIONS

Ninety patients with skeletal tuberculosis, forty of whom were treated without streptomycin and fifty of whom were given at least one course of streptomycin in a daily intramuscular dose of twenty milligrams per kilogram of body weight for ninety-one days, were observed for a fifteen-month period.

The small numbers in the control and streptomycin groups limit the conclusions which may be drawn from the findings, namely that:

1. On the basis of x-ray evidence alone, the condition of the control and streptomycin groups was essentially the same; more than four-fifths of the patients in each group showed improvement roentgenographically at the end of fifteen months.

2. On the basis of the patient's condition as judged by x-ray and clinical data combined, there was a definite superiority among the streptomycin-treated patients. At fifteen months only 72 per cent. of the control group evidenced improvement, whereas improvement was noted for 79 per cent. of the streptomycin group as early as three months and for 89 per cent. of this group at fifteen months.

3. The action of streptomycin appears to produce a generalized effect upon the well-being of the patient with skeletal tuberculosis, and upon the secondary manifestations of the tuberculous process as illustrated by cessation of sinus drainage, reduction in the sedimentation rate, return towards a normal hemoglobin level, and evidence of greater improvement in functional ability.

* Although it is not the consensus of the cooperative group, Dr. Samuel Kleinberg and Dr. Barnard Kleiger who contributed fifteen of the ninety patients reviewed in this paper believe that a word of caution should be added: "Namely, that patients who have an isolated osseous tuberculous lesion, but who are otherwise in good general condition and have no complications or secondary effects due to tuberculosis, should not be treated with streptomycin. Then, if at a later date serious complications develop, the drug may be used with unimpaired efficiency".

DISCUSSION

DR. RALPH K. GHORMLEY, ROCHESTER, MINNESOTA: These reports cover something over 750 cases, according to my estimate. These papers seem to be well deserving of considerable study, and I hope that our *Journal* will publish all of them together, so that every one of you may read them in detail. Undoubtedly you will come to some conclusions which are different from those I have been able to draw.

Before I go further, I must say in behalf of the panel which worked on the Public Health Service group of cases that we should express our appreciation to those physicians and statisticians in Washington who have done so much to make the panel reviews easy. The amount of work which they put on this is prodigious; collecting and cataloguing material and facts from a widespread group of hospitals and getting the

data together in such shape that they can be readily looked over within a day or two by a small group of us is no small task. I think their work should be commended. Dr. Murray and Mrs. Rosen, of the Public Health Service, happen to be here today; as far as I know, none of the Central Office group of the Veterans Administration are here, but both groups deserve a great deal of credit.

All of us will agree, I think, that benefit is derived from the use of streptomycin. Just how far one may go with such a statement remains to be seen. The results in the Public Health Service group of cases, as Dr. Moore has pointed out, have been reviewed only for periods ranging up to fifteen months; another review, set for this summer, should enable us to see much better what real improvement has come from the use of streptomycin.

The group of cases from the Veterans Administration has been under observation longer and probably represents less serious disease than does the Public Health Service group, which includes the more advanced cases from Alaska, and Dr. Bosworth's series from New York. The Veterans Administration group does have some cases of advanced disease, but in many instances the condition was diagnosed early and the treatment, therefore, has been more effective.

It is apparent, I think, that streptomycin alone has not proved so effective as streptomycin combined with surgical measures. Just exactly what surgical procedures should be carried out in many of these cases may be debatable. I hope that time and further observation of these cases will supply information which will make it possible to set up some definite program for surgical treatment, although such treatment will always have to be varied according to the case.

Observations based on roentgenograms alone obviously are not of any value up to a year or even fifteen months after treatment in most instances. Roentgenographic changes are slow to take place. Even after the healing of the soft tissues, healing of bone, as evidenced in roentgenograms, cannot be seen for some months. The Veterans Administration group of cases is in its third year of observation, and in those cases it has been interesting to see the changes noted in the latter part of the observation period as compared with those in the first months.

It is important to prove the diagnosis in any such study as this. In setting up the Veterans Administration group, we insisted that only proved cases be accepted. That was not always possible in cases of spinal tuberculosis, and cases of spine involvement in which we had some doubt whether the cause was tuberculosis were thrown out.

Surgical treatment is certainly easier and safer when carried out in conjunction with streptomycin therapy. The drainage of abscesses alone is not adequate, as Dr. Bosworth has pointed out, and certainly osseous lesions must be treated also by fixation. Sooner or later most osseous lesions have to be treated by surgical stabilization, if the healing is not accomplished by conservative means.

I was also interested in Dr. Bosworth's attitude on the toxicity of streptomycin and his feeling that, while deafness developed in five or six patients of his group, he is not worried about it, because the tuberculosis is arrested. There is plenty of basis for argument on his side. I do think, though, that with adjustment in the dosage, these toxic manifestations probably can be reduced.

I agree with Dr. Moore about sensitivity tests—they are not very reliable. It is difficult, of course, to carry them out in most cases of bone and joint tuberculosis, and probably most of us who have been able to get such tests have not always felt that we could rely on the results. Nevertheless, when they can be made easily, it is well to have them and to put the results on the record, so that the data may be analyzed at some time.

Finally, I express the hope that the day will come when early diagnosis can be made in tuberculosis. Certainly, if a lesion, even a small one, is suspected of being tuberculous, then a real effort should be made to establish the diagnosis, because only early in the disease can the best results with the use of streptomycin be obtained.

As Dr. Moore indicated, we cannot say that any tuberculous lesion, for instance one in a weight-bearing joint, is cured. We have had more than 200 lesions under observation for perhaps three years. They seem to be arrested by treatment with streptomycin. Nevertheless, we should not conclude that such lesions are cured until they have been carefully observed over a long period of time.

Dr. Alan De Forest Smith, New York, N. Y.: Dr. Horace Yu and I treated and reviewed a small series of cases which were reported two years ago and we have continued to study them and some additional cases since that time. Our group represented a selected one, in that we did not admit any patients who had active pulmonary tuberculosis; and the patients in this group were not so seriously ill as the group of patients whom Dr. Bosworth treated. His cases were selected too, but they were selected as being the most severe cases that one could deal with, and I think that the use of streptomycin has had its most severe test in that group of cases and perhaps in those that Dr. Moore had in Alaska. We have used, in addition to an average of one gram of streptomycin a day, para-aminosalicylic acid in our later cases. We erred in our earlier cases in not continuing streptomycin long enough. We are now using it over a much longer period than we did in the beginning. There were two reasons for not continuing the use of streptomycin longer in the earlier

(*Continued on page 329*)

THE TREATMENT OF TUBERCULOUS BONE DISEASE BY SURGICAL DRAINAGE COMBINED WITH STREPTOMYCIN*

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Conservative therapy of bone and joint tuberculosis has been the accepted method of management, and surgical textbooks have stressed it as the keystone of treatment for over fifty years. Adequate warning against any radical or surgical measures has been summarized by Dickson in the following statement: "Introducing a drainage tube into a tuberculous abscess makes certain that a draining sinus will form, which will become secondarily infected and which will probably never heal. It has been truly said that draining a tuberculous abscess frequently signs the patient's death warrant."

The discovery of the bactericidal properties of streptomycin, including its suppressive action against the *Mycobacterium tuberculosis*, by Schatz, Bugie, and Waksman in 1943, has changed our concepts of the handling of many tuberculous lesions. Early reports [2,4,5] on its effectiveness in skeletal tuberculosis were disappointing and unpromising. This was particularly true when treatment was carried out with the use of the antibiotic alone, without concomitant surgical procedures. As the years passed, however, more encouraging and at times most gratifying results have been reported in the literature. Among the more striking of these are those of Morgan and Bosworth [8] and Brock in the treatment of draining sinuses, Winterhoff and Weber, Harken and his associates, and many others. The report of Bosworth and his associates [1] on the high percentage of closures of pre-existing sinuses, and the experience of Smith and I-Sen Yu with combining streptomycin and surgery have made the outlook for arrest and control of this distressing disease more favorable.

Whereas most previous reports have dealt with the effectiveness of streptomycin in producing closure of pre-existing sinuses, or have shown the pronounced effect of the antibiotic in facilitating surgical fusion of affected joints, few cases have been reported in which abscesses and bone lesions have been surgically opened and drained, and in which joint motion has been retained and encouraged.

The purpose of this study is to present the effect of streptomycin in conjunction with the surgical incision of abscesses, débridement of the lesion, and its conversion to a freely draining sinus by the use of gauze packing. The method was applied in a series of lesions, most of which were in patients who had not been previously treated and who had no pre-existing draining sinus from a treated lesion. Aside from the fact that these were all "closed" lesions, the series was otherwise unselected. It is, so far as we know, the largest series of such cases reported, with the longest period of follow-up. The first patient was operated upon in October 1946, and the last in April 1950. Since that date many more patients have been treated in a similar manner, with similar gratifying results.

We recognize the fact that the series is numerically insignificant and that the period of observation has not been long enough to throw any light on the future prognosis of a chronic disease as prolonged and unpredictable as tuberculosis. In tuberculosis the individual variants are great. Progression of the lesion as seen by roentgenogram, the individual host response, and the results of therapy are difficult to prognosticate and standardize. Early experience is not always supported by later knowledge and accumulated observations; however, opinion must be formulated from current knowledge, drawn from the fund of numerous cases treated by streptomycin alone, and compared with cases treated before the advent of this antibiotic, both in our personal experience and in the reported experience of others. We have been led to a changing concept of the principles

* Based on an exhibit at the Annual Meeting of The American Academy of Orthopaedic Surgeons, Chicago, Illinois, January 27 to February 1, 1951.

of treatment of skeletal tuberculosis. The results have been so much better than those obtained in earlier years that we consider them remarkable, and feel that, if the late results and further experience bear out the findings in this series, the principles of therapy of bone and joint tuberculosis will be radically changed.

CLINICAL MATERIAL

Fifty-two patients were treated between October 1946 and April 1950. They presented sixty-three lesions which were treated according to the methods and principles to be described. Cases were unselected except for the stipulation that they represent closed lesions, and no patients were discarded from the study because of age, physical condition, location of lesion, other pre-existing and co-existing "open" lesions, or other factors. The age range was from one to seventy-two years; nine patients were children under the age of sixteen and forty-three were over sixteen; thirty-four were white and eighteen Negro; twenty-six were male and twenty-six female. Duration of lesions varied from apparently recent acute infections to chronic lesions of long standing. Many patients had concomitant pulmonary lesions and were hospitalized in a tuberculosis sanatorium which restricted admissions to patients with pulmonary involvement. We believe that, for this reason, numerous bone lesions were diagnosed early, because particular attention was given

TABLE I

LOCATION OF LESIONS

Spine	
Cervical vertebra	1
Thoracic vertebrae	
With paralysis	3
Without paralysis	5
Thoracolumbar region	4
Lumbar vertebrae	11
Sacro-iliac joint	6
Ilium	4
Hip	4
Knee	5
Ankle	3
Foot	1
Shoulder	3
Ribs	3
Elbow	1
Wrist	4
Sternoclavicular joint	5
Total Number of Lesions	63

to unusual complaints, and because physical and roentgenographic examinations were made to determine the possible existence of early lesions. It was of particular interest to note the frequency of early minimal complaints accompanied by well-established and even advanced lesions as shown by roentgenographic findings. The anatomical distribution of the lesions is shown in Table I.

The diagnosis of the lesion was established in the majority of cases by guinea-pig inoculation, culture, or direct smear. In the remaining few, histological section, roentgenographic findings, history, physical findings, and laboratory tests were sufficiently convincing to leave no doubt of the diagnosis.

INDICATIONS FOR OPERATION

It is believed that all patients exhibiting one or all of the following characteristics

should be subjected to surgical intervention and to the principles of treatment to be outlined. These indications are:

1. Progressive advancing tuberculous bone lesion.
2. Abscess formation as evidenced by clinical or roentgenographic findings.
3. Sequestrum formation.

We do not believe that all patients with tuberculous involvement of bone should be immediately subjected to radical surgery. Frequently the patient is first seen and the diagnosis is made while the lesion is in a quiescent or even healing stage. Early involvement of the spine, particularly in children, with evidence that the infection is static, can often be arrested by conservative means, such as immobilization in a cast or brace, without long periods of complete recumbency. Thoracolumbar lesions would appear to be most amenable to conservative treatment by immobilization, provided no evidence of abscess formation or sequestrum formation is present. Lesions in the lower lumbar region, which are more difficult to immobilize, and lesions of the upper thoracic region, in which there is the potential danger of spinal-cord involvement, are probably best handled by the more radical procedure of sequestrectomy, drainage, and packing, unless good evidence of healing becomes apparent without preliminary progression of the lesion. Each patient must still be closely studied and individually evaluated.

In patients seen early, in whom deformity has not yet developed, prevention of deformity must be the chief aim. The long-range outlook for success in the handling of tuberculosis cases is the application of these principles to the patients in whom diagnosis is made early, putting an end to the advance of the infection and preventing deformity. The deformity results not only from the changes in bone configuration but, as often, from secondary muscle spasm and contracture.

Patients first seen when the condition is in an advanced stage and deformity has developed must first be made inactive, and progress of the disease must be completely arrested. Although additional procedures may be required for functional improvement, initial handling of the case according to the following principles of treatment is deemed advisable to halt the activity of the disease, to prevent long periods of recumbency and invalidism, and to ensure the success of future procedures which may be considered necessary.

PRINCIPLES OF TREATMENT

1. *Adequate Open Drainage*

The keynote of successful treatment has been the adequate drainage of the tuberculous lesion coupled with streptomycin therapy. Sound surgical procedures, following those accepted for treatment of pyogenic osteomyelitis and septic arthritis, are essential, and failure can usually be traced to a disregard of these surgical principles. Inadequate drainage, failure to make a large enough incision, failure to remove sequestra, and too early removal of packing are believed to be the pitfalls leading to failure of healing. Conversion of an abscess and its bone lesion to a freely draining sinus is a cardinal principle in treatment, and is essential before streptomycin can be used successfully.

2. *Removal of Sequestra*

Accumulated pus, necrotic and caseous material, and loose fragments are removed from the region of bone destruction. No curettage of the surrounding soft bone is done, as this bone represents an intact matrix which will subsequently become calcified and vascular.

3. *Conversion of Abscess to a Freely Draining Sinus with Gauze Packing*

The area from the bone lesion to the skin is packed snugly with plain or iodoform gauze. The gauze is not used as a drainage medium but is intended to form a cone-shaped sinus from the lesion outward. It is left intact for twelve to fourteen days and is then removed altogether. Anaesthesia is not usually necessary for removal of the packing and no

repacking of the sinus is done. Superficial bleeding from the granulating sinus tract may be easily controlled by light gauze implantation for a few minutes. The sinus is then left to close spontaneously and only superficial dressings are applied.

4. *Administration of Streptomycin*

Streptomycin, one gram per day intramuscularly, is started on the day of the operation and is continued for a period half as long as the time required for closure of the sinus. The streptomycin is given in a single dose daily and is most frequently administered by a member of the family or a visiting nurse after the patient has gone home. In this series, streptomycin was not given preoperatively, because of the increased possibility of toxicity and the earlier production of streptomycin resistance in the organism. Although combinations of para-aminosalicylic acid or amithiozone with streptomycin were not used, there is no contra-indication to their use; they may, in fact, enhance the antibiotic effect. Streptomycin is preferred to dihydrostreptomycin, because of its greater effectiveness and because toxic reactions to streptomycin tend to stop with cessation of the drug, whereas toxic reactions to dihydrostreptomycin tend to be progressive beyond cessation of the drug.

5. *Splinting of Joints Postoperatively*

Although many patients will not require it, splinting for comparatively short periods may be done for control of pain, until the packing has been removed and the patient is comfortable. In tuberculous bone and joint infections, pain does not tend to be marked when relief of pressure from an abscess has been obtained.

6. *Encouragement of Active Motion in Peripheral Joints*

When good joint motion in weight-bearing joints has been attained, the patient is allowed light weight-bearing on crutches. The degree of weight-bearing is increased if it is tolerated without symptoms.

7. *Improvement in General Nutrition and Treatment of Anaemia*

High-caloric and high-vitamin diets and the use of transfusions and hematinic drugs are ordered as indicated.

8. *Dihydrostreptomycin in Cases of Toxic Reaction to Streptomycin*

If signs of a toxic reaction to streptomycin develop, the drug should be discontinued for two or three weeks until signs of toxicity regress. Dihydrostreptomycin should be administered cautiously thereafter.

DOSAGE OF STREPTOMYCIN AND TOXICITY

In the early cases, the dosage of streptomycin was high, as we were following the accepted trend of three grams daily when the drug was first used clinically. Gradually, it became apparent that smaller doses were equally effective and produced less toxicity. The greatest amount of information was gained by observing the response of patients with tracheolaryngeal lesions, of whom there were many in the sanatorium, since a direct view of the changes could be obtained in these lesions. It soon became evident that response was as good with a daily dosage of one gram or even 0.8 gram, and that divided daily doses were not necessary. With the decreased dosage, toxic manifestations of vertigo, tinnitus, loss of hearing, and nausea became less frequent. Although daily dosage of a single intramuscular injection of one gram has been maintained throughout this series and no concomitant administration of para-aminosalicylic acid or amithiozone has been used, evidence is now accumulating to show that equally good or better results may be obtained when these drugs are used and the interval between doses of streptomycin is increased to two or even three days. With this latter regimen, toxicity is practically non-existent, and

the length of time before streptomycin resistance of the organism develops is increased to at least two or three times that which occurs with daily administration.

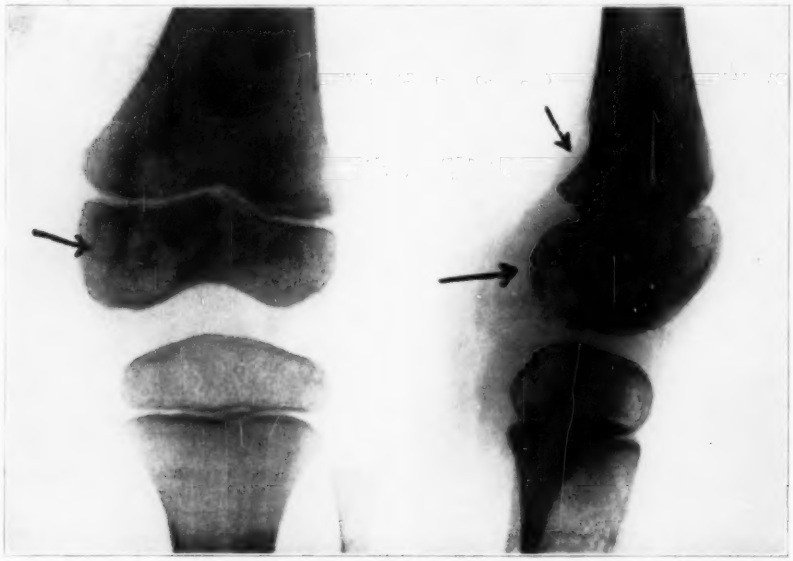

FIG. 1-A

Case 4, J. M. April 19, 1947. Roentgenograms made two days before the lesion was opened and packed. The diagnosis was confirmed by guinea-pig inoculation.

FIG. 1-B

November 3, 1949. Six months after the operation healing appeared to be complete both clinically and roentgenographically. Serial roentgenograms over a period of two and one-half years revealed no growth disturbance.

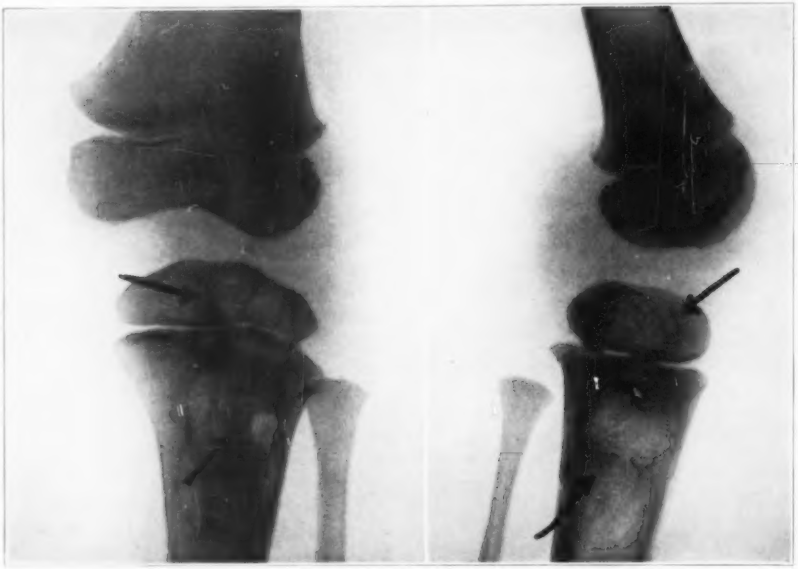

FIG. 2-A

Case 11, R. R. July 29, 1947. There was involvement of proximal portion of the tibia with marked soft-tissue and knee-joint swelling and thickening.

FIG. 2-B

Fig. 2-B: December 3, 1947. Four months after the operation. The patient, aged two years, has been bearing full weight for about one month and is completely asymptomatic.

Fig. 3-A: Case 19, M. V. April 14, 1948. This eleven-month-old girl had been treated with splinting and streptomycin for almost five months before this roentgenogram was made. There was concomitant pulmonary tuberculosis and tuberculous meningitis with gradual recovery.

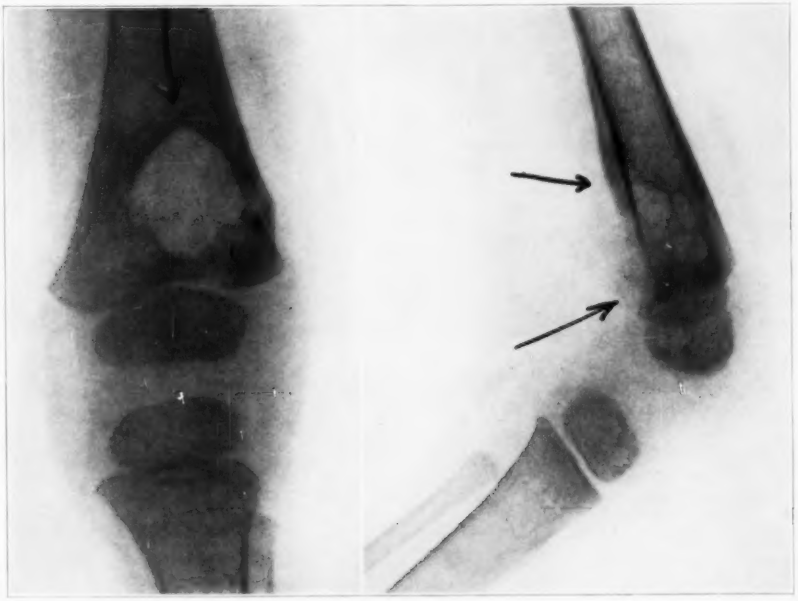

FIG. 3-A
(*See p. 304*)

FIG. 3-B

October 24, 1948. The roentgenogram showed excellent healing. There was no disturbance in epiphyseal growth and the patient had a full range of painless motion.

FIG. 4-A

FIG. 4-B

Fig. 4-A: Case 7, D. B. May 4, 1947. The patient had marked pain, swelling, and limitation of motion of right shoulder.

Fig. 4-B: November 14, 1947. Note re-establishment of the roentgenographic configuration of the epiphysis and epiphyseal plate within six months after operation. Recovery was maintained both clinically and roentgenographically without growth disturbance until the patient's accidental death in July 1950.

Streptomycin calcium chloride complex has been used in the majority of cases, and dihydrostreptomycin was resorted to in only three instances. Occasional vertigo has occurred, but only in two instances was it severe enough to call for discontinuance of the drug.

Case 26: A white female (A. S.), aged thirty-seven, with knee-joint involvement, had toxicity of such severity that the drug had to be discontinued eighteen days after operation. No loss of hearing occurred. Dihydrostreptomycin was not available at that time; it was used about one year later, however, when a surgical arthrodesis was performed because of progressive destruction of the knee, despite continuous immobilization in a cast.

In a second case, extreme vertigo developed in a white male (Case 9, R. S.), aged twenty-eight, with multiple involvement of both hips, both knees, and of the spine since early childhood. An abscess of the lower thoracic portion of the spine had been drained by costotransversectomy. After a period of a few weeks of rest, the vertigo subsided fairly well, and dihydrostreptomycin was begun with a daily dosage of one gram. Although there was only a minimal increase in vertigo, complete loss of high-pitched tone reception was noted after a short while; the antibiotic was discontinued, but the loss of hearing progressed over a period of three months to a total loss of 45 per cent. by audiometric tests. The surgical sinus had closed and remained closed.

A third patient (Case 4, J. M.), a white female child, aged three and one-half, presented painful local swelling in the deep and superficial tissues at the sites of injection, which necessitated substituting intermittent short courses of streptomycin. Healing of the knee lesion progressed without any untoward effect, and full recovery was demonstrable both clinically and by roentgenogram.

In the past two years we have seen practically no toxic manifestations of the drug, and are of the opinion that better methods of purification are decreasing the dangers so evident in its earlier use. This conclusion is based on observation of hundreds of patients with pulmonary tuberculosis treated at the sanatorium, in addition to our own patients with bone and joint involvement.

As to the length of time of administration, there was little data to guide us in the early cases. Generally, streptomycin was continued for short periods beyond the time of closure of the sinuses. As observation progressed, a principle was established [3] to continue the antibiotic for a period half as long as the time required for the sinus to close. The decision is completely arbitrary, but clinically it works well; in those few cases in which

there was recurrence of drainage, though minimal, the drug had been withdrawn shortly after closure of the surgical sinus. In those cases, administration of additional doses of streptomycin produced eventual closure of the sinus, although this proceeded more slowly than closure of the original surgical sinus.

ANALYSIS OF CASES

Lesions in Children

In view of the varying factors to be considered—of structure, growth, healing response, previous exposure to tuberculous infection, immunity response, *et cetera*—in children as compared with adults, it was believed advisable to evaluate these cases separately. There were nine children—that is, patients under sixteen years of age—in this series. Of those with peripheral lesions, all showed the characteristic of the lesion beginning in the metaphysis or epiphysis, adjacent to the epiphyseal plate, with destruction

FIG. 5-A

Case 45, M. C. S. March 21, 1950. Streptomycin and traction for three weeks before this roentgenogram was made had no apparent effect on the progressive destruction.

FIG. 5-B

October 8, 1950. Six and one-half months after surgery, the child, aged two, was walking normally and presented no abnormal objective findings.

FIG. 6-A

FIG. 6-B

Fig. 6-A: Case 13, C. M. October 3, 1947. This girl, aged thirteen, had been under treatment for six years and had been wearing a caliper weight-bearing brace for four years. Note calcification in large pelvic abscess, which was later incised and drained at the time of hip surgery.

Fig. 6-B: January 7, 1951. Although arthrodesis appears to have occurred, there is a moderate range of functional hip motion. At the time this roentgenogram was made, the child had been fully active for almost three years without clinical or roentgenographic signs of reactivation.

spreading across the epiphyseal plate and extending into the joint. When the lesions were diagnosed early, the synovial membranes of the joint hardly appeared to be affected. When extension had progressed further, thickening, inflammation, intra-articular exudate, and granulation were present, with marked intra-articular swelling and tension.

The surgical procedure consisted essentially in opening the most direct approach to the bone lesion. This approach was usually determined by the localization of the soft-tissue fluctuation, and opening this superficial abscess yielded a tract directly to the lesion. This was particularly the case in lesions about the knee and shoulder. Hip lesions required anatomical dissection through an anterolateral incision overlying the greater trochanter, opening of the distal joint capsule with anterior splitting, and exposure of the neck and head of the femur.

CASE 4: J. M., a girl, three and one-half years of age, was admitted to the hospital on April 17, 1947, with a history of intermittent pain in the left knee for about one year. She had previously been treated at another hospital with penicillin and her tonsils and adenoids had been removed. She had worn a cast for two months and was then given physical therapy. When she was first seen by the authors, the knee was swollen, warm, tender, and markedly limited in motion because of pain. Roentgenograms showed a large ovoid area of bone destruction at the medial aspect of the distal end of the femur, crossing the epiphyseal plate and breaking through the joint surface posteriorly (Fig. 1-A). On April 21, 1947, the lesion was opened through a posteromedial approach, the large cavity was cleared of necrotic and granulation tissue, and gauze packing was inserted. The synovial capsule of the knee joint showed only moderate inflammatory changes. Diagnosis was confirmed by guinea-pig inoculation. A cast was applied. The drainage persisted until August 7, 1947, when daily dosage of one and one-half grams of streptomycin was begun. On September 13, 1947, it had to be discontinued because of severe local reaction, but the sinus had closed on September 1, 1947. In October 1947, because of normal range of motion and no abnormal findings, the cast was discontinued and the child was allowed full weight-bearing. Roentgenograms demonstrated that healing was progressing remarkably. A second course of streptomycin was given between November 13 and November 24, 1947, but was again discontinued because of local reaction. To the present time, five years since the operation, there have been no signs of abnormality or disturbance in normal growth of the femur (see Figure 1-B).

Two similar cases, one a two-year-old girl (Case 11, R. R.) with involvement of the proximal end of the tibia, and the other an eleven-month-old child (Case 19, M. V.) with a similar abscess of the distal end of the femur, were treated in like manner.

CASE 11, R. R. In this patient the sinus healed in twenty-six days, although one gram of streptomycin daily was given for ninety-three days because of a concomitant pulmonary lesion. The child began full weight-bearing in October 1947, about three months after the operation, and when last seen was completely asymptomatic and showed no evidence of growth disturbance (Figs. 2-A and 2-B).

CASE 19, M. V. In this case the knee had been put in a splint and streptomycin had been administered for a period of almost five months before operation because of tuberculous meningitis and pulmonary tuberculosis. Despite this, progressive bone destruction in the distal end of the femur occurred and extended into

FIG. 7-A

Case 5, R. K. April 2, 1947. There was marked swelling, pain, and limitation of motion. Through-and-through drainage was done from radial to ulnar side.

FIG. 7-B

December 30, 1950. The patient had had asymptomatic full function and motion for three years. The wrist had been immobilized in a cast for about six months after the operation.

Fig. 8-B

Fig. 8-D

Fig. 8-A

Fig. 8-C

(*Legends on page 311*)

Fig. 8-A: Case 15, T. W. January 17, 1948. A localized tuberculous tendovaginitis of thumb extensor had been drained and the sinus closed, but severe wrist pain upon motion persisted. The wrist was placed in a cast, and streptomycin was continued.

Fig. 8-B: April 15, 1948. Serial roentgenograms showed progressive destruction despite wrist casts and continued dosage of streptomycin.

Fig. 8-C: July 17, 1948. Destruction continuing. At this point débridement and packing were done.

Fig. 8-D: December 9, 1948. The sinuses had closed and the patient had regained about 80 per cent. of motion and strength of the wrist. No further destruction or activity of infection were noted at follow-up examinations.

the knee joint (Fig. 3-A). Following surgical curettage and packing in April 1948, and additional streptomycin for thirty-three days, there was rapid improvement both clinically and roentgenographically. The sinus closed twenty-eight days after the operation. Full range of motion and normal growth have been retained (Fig. 3-B). General muscle strength and coordination were gained gradually and the child was walking without assistance in February 1949.

The capacity for regeneration in large areas of bone which appear to have been destroyed, as well as the capacity to re-form a normal appearing and growing epiphyseal plate is strikingly demonstrated in the following case.

Case 7, D. B., aged three, had been a patient at the tuberculosis sanatorium for treatment of a diffuse pulmonary involvement since October 5, 1945. In April 1947, he was seen after a fall in which he struck the right shoulder. There was local swelling, but no pain, tenderness, or limitation of motion. Roentgenographic findings were negative. Symptoms progressed, with increased swelling, pain, and limited motion, and a roentgenogram made on May 4, 1947, showed a large destructive lesion involving the proximal epiphysis, epiphyseal plate, and the tuberosity of the humerus (Fig. 4-A). Incision, curettage, and gauze packing were done that day. The swelling and drainage subsided rapidly during a course of one and one-half grams of streptomycin given daily; closure of the sinus occurred in five weeks. Streptomycin was continued for eighty-seven days, because of the beneficial effect noted on the pulmonary lesion. Unfortunately, the child was killed by an automobile about July 1950, but until that time he had shown no abnormal findings referable to the shoulder and had maintained normal growth during the three-year period (Fig. 4-B).

Fig. 9-A

Fig. 9-A: Case 31, D. H. May 23, 1949. Extremely painful ankle, with large, fluctuant soft-tissue abscess medially and laterally. Incision and packing of both sides of ankle joint.

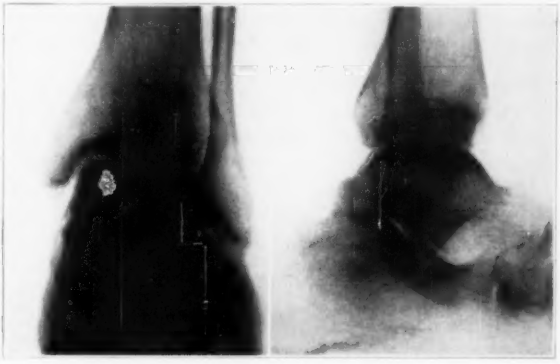

Fig. 9-B

Fig. 9-B: December 7, 1949. Patient had been fully weight-bearing for three months. There was a full range of motion and the sinuses were closed.

A more recent case, with striking and rapid healing demonstrable clinically and by roentgenograms, presented involvement of the hip joint in an infant.

Case 45, M.C.S. This patient, a girl aged one and one-half years, was seen on January 4, 1950, with

signs of pain and spasticity of the left hip. A diagnosis of tuberculosis was made. A daily dosage of one gram of streptomycin was given for three weeks and traction was applied. Roentgenograms showed continued progress of the lesion and there was no improvement clinically (Fig. 5-A). On January 26, 1950, incision, curettage, and packing of the lesion were done. A cast was applied but was removed four weeks after the operation, at which time the incision was healed and no abnormal objective findings were present. Streptomycin was given daily for six weeks from the day of operation. Complete range of motion, full weight-bearing, and roentgenographic evidence of complete healing of the lesion have continued to the present (Fig. 5-B).

This case again shows the failure of streptomycin alone to control the destructive lesion. We feel certain that the surgical intervention has probably saved this child years of treatment which might have ended in a fused hip with marked shortening and disability, the most frequent result of presently accepted methods of treatment.

In contrast with the foregoing case is that of a thirteen-year-old Negro child with a history of previously existing tuberculosis of the hip following a fall in 1941.

Case 13, C. M. This patient was first seen in the tuberculosis sanatorium in 1947 wearing a caliper limb brace which had been fitted in 1943, following almost two years of treatment for acute tuberculosis of the right hip according to generally accepted principles of treatment. Her pulmonary lesion was well controlled, although she presented marked cervical adenitis on the right. There was a marked foot-drop on the right because of the constant use of the brace. Shortening of one and three-fourths of an inch was present. Roentgenograms showed marked destruction of the femoral head and neck and of the acetabulum, and there was evidence of a large calcifying pelvic abscess (Fig. 6-A). On November 3, 1947, an operation was performed, primarily for the purpose of doing a hip fusion. During exposure of the hip joint, large quantities of free pus and caseous necrosis were encountered, and the pelvic abscess was entered in two areas, because of a tissue-thin acetabular and iliac wall. Under pressure about 500 cubic centimeters of pus was evacuated from the pelvis and rubber tubes were inserted into the cavity. The hip lesion was packed with gauze, and the hip was immobilized in a plaster spica. Streptomycin was given intramuscularly, one gram daily for seventy-six days. Packing and tubes were removed after twelve days. The sinuses were closed in fifty-two days. Spontaneous fusion was hoped for, but on removal of the cast on July 20, 1948, there was painless motion of 60 degrees of flexion, 10 degrees of abduction and adduction, 10 degrees of internal rotation, and 5 degrees of external rotation. Shortening was compensated for by a shoe lift of one and one-half inches and the child has been bearing full weight painlessly and attending school daily without clinical or roentgenographic evidence of reactivation of the lesion or further destruction of the hip (Fig. 6-B).

Peripheral Joint Lesions

Excluding lesions of the spine, sacro-iliac joints, ribs, ilium, and sternoclavicular regions, there were twenty-one involvements of freely movable peripheral joints. Of these, the six which occurred in children have already been discussed.

Four cases of wrist involvement occurred among adults.

Case 18, W. H. had old destruction of most of the carpal bones with spontaneous fusion, but marked swelling and pain as a result of continued infectious activity. The wrist was in about 15 degrees of volar flexion. Operation consisted in incision and evacuation of caseous, purulent material, curettage of the area, and forcible gradual manipulation into about 10 degrees of dorsiflexion. The sinus closed in eighteen days. Immobilization in a cast for three months resulted in fusion and the patient became symptom-free.

The remaining three patients (Case 5, R. K.; Case 43, W. S.; and Case 15, T. W.) maintained excellent to good motion, despite marked carpal destruction in two of these (Figs. 7-A and 7-B, and 8-A to 8-D).

There were three cases with involvement of the ankle joint. In one the diagnosis was made by the laboratory, following a fusion procedure for what was thought to be a non-specific infectious arthritis. Streptomycin was administered for thirty-six days, and solid fusion and closure of a sinus which had developed spontaneously after the operation were obtained. The other two patients were treated by routine procedures, which resulted in asymptomatic joints with full range of motion, full weight-bearing, and roentgenographic evidence of healing (Figs. 9-A and 9-B).

The single case of foot involvement was handled by resection of portions of the mid-tarsal bones. Fusion did not occur, but good motion and full weight-bearing was attained.

Both of the patients with involvement of the hip had excellent end results, although in one the process was of two years' duration; in the other, onset had been very recent.

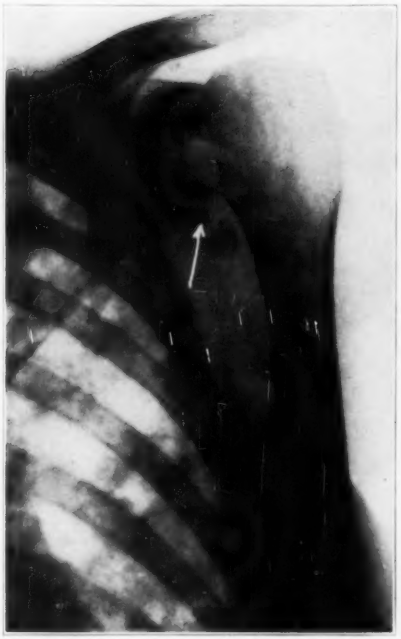

FIG. 10-A

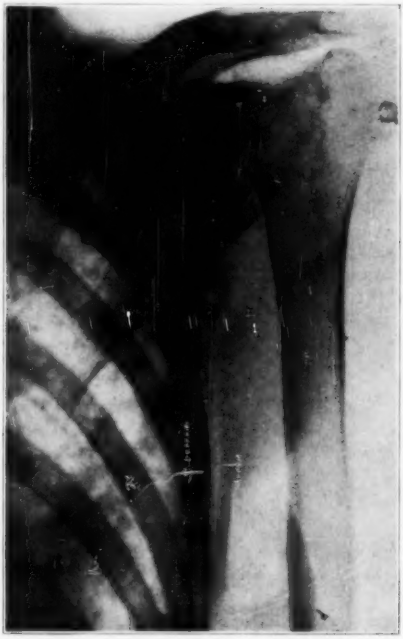

FIG. 10-B

Fig. 10-A: Case 34, B. B. March 26, 1949. Very large soft-tissue abscess extending almost to the elbow joint. The surgical approach was made directly to anterior aspect of the shoulder joint; a tube for drainage was inserted in the distal third of the arm.

Fig. 10-B: January 7, 1951. No further progress of destruction had occurred at this time, almost two years after the operation. The patient had about 50 per cent. of shoulder motion without pain.

Figures 10-A and 10-B (Case 34, B. B.) show the cessation of destruction in a shoulder. The process had been rapidly progressive before surgical drainage, despite administration of accepted dosages of streptomycin for a severe co-existing pulmonary lesion. Notwithstanding the destruction of bone, motion of about 50 per cent. of normal and freedom from pain and inflammatory signs have been maintained for the past three years.

It is surprising that only one case of tuberculosis of the knee in an adult was seen during the period of this report (this was Case 26 discussed under the heading, "Dosage of Streptomycin and Toxicity"). Only a single case of tuberculosis of the elbow was treated, and the response was favorable, with retention of about 25 per cent. of active motion, but no progression of destruction or disabling pain.

To sum up, one pre-existing spontaneous fusion was treated, three surgical fusions were performed in adults, and eleven peripheral joints were treated by the routine procedure, no arthrodeses being performed. Motion was encouraged as soon as it was tolerated, and gradual weight-bearing was allowed in the lower extremities as soon as absence of pain and abnormal objective signs were noted. Despite roentgenographic evidence of destruction in some of these peripheral joints, good painless motion was generally attainable and no reactivation of infection has so far been evident.

Sacro-Iliac Joint Lesions

All six patients with sacro-iliac lesions responded in the same manner, although two somewhat different procedures were used. Some of these lesions were treated by curettage and plain gauze packing, while in others chips of bone from the posterior iliac crest were

implanted, followed by gauze packing from that area to the skin. It is essential to explore surgically from a localized bone abscess of the sacrum or ilium into the joint itself and to debride it thoroughly if the cartilage is found to be softened or if granulation tissue and necrosis are present. Packing should usually be extensive. Spontaneous fusion has occurred in most of the cases, but does not seem to be dependent upon placement of graft material (Figs. 11-A to 11-D). No immobilization was used except a corset, if the patient desired

FIG. 11-A

Case 14, L. S. May 5, 1948. The patient presented an abscess overlying the left sacrum, which was superficially incised and drained. Diagnosis of tuberculosis was confirmed by guinea-pig inoculation. Despite streptomycin, drainage persisted and there was roentgenographic evidence of progressive destruction.

FIG. 11-B

October 18, 1948. Pantopaque was injected into the sinus through a small catheter. Note on the lateral roentgenogram (Fig. 11-C) that destruction extends through the sacrum and that both ilium and sacrum are involved. Thorough débridement and packing were done.

one, and activity was resumed as soon after removal of the packing as the patient felt willing. One patient (Case 47, B. P.) returned with a recurrent pin-point sinus, which closed after additional dosage of streptomycin. She went through a full-term pregnancy without any disturbance or reactivation of the lesion (Figs. 12-A and 12-B), despite the fact that she conceived only two months after the operation for the sacro-iliac lesion.

Involvement of the Spine without Paraplegia

These constitute the largest group of cases in the series; there were twenty-one lesions. Only one patient with involvement of the cervical portion of the spine was treated (Case 38, A. H.), and the end result was excellent, there being only some restriction of rotation to the left, and extension beyond neutral position (Figs. 13-A to 13-D). The abscess was so large that it resulted in pressure obstruction of the trachea with unconsciousness; the patient's life was saved by an emergency tracheotomy. Following drainage of the lesion in July 1949, healing was uneventful. However, despite a long course of streptomycin and amithiozone, a lesion of the anterior portion of the left first rib subsequently developed, then a lesion of the left knee (proximal end of the tibia), and following this a severe destructive lesion of the left shoulder. This last

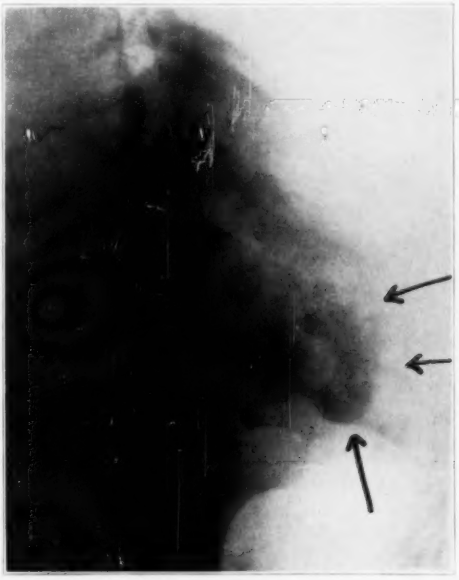

FIG. 11-C

FIG. 11-D

July 17, 1949. At this time the sinus had been closed for over seven months and the patient was asymptomatic.

FIG. 12-A

Case 47, B. P. February 10, 1950. Early lesion demonstrated about six weeks after onset of pain. Repeated roentgenograms made previously had been negative.

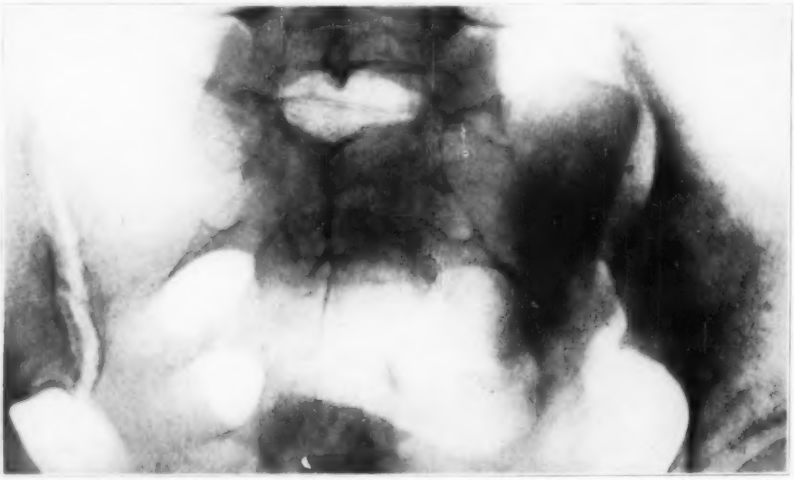

FIG. 12-B

January 11, 1951. Uneventful healing following routine surgery and streptomycin. The patient carried through a full-term pregnancy; normal delivery had taken place about four weeks before this roentgenogram was made. No reactivation was noted at follow-up examination.

lesion was still under treatment in March 1952, but was progressing well. All the other lesions appear to be healed.

Not all of the nine lesions of the thoracic and thoracolumbar regions were accompanied by paraspinal abscesses. In three cases, no encapsulated pus was encountered, but treatment was carried out in the routine manner. Healing progressed in like manner in all cases, to closure of sinuses and freedom from symptoms, with roentgenographic evidence of healing. In most cases, immobilization in a cast or brace was maintained for about six

months after operation. In some, spontaneous fusion occurred. In others, there was merely recalcification of the vertebral body with maintenance of disc space and probably limited motion. Clinically, there appeared to be no difference in the end result.

The cases of lumbar lesions roughly divide themselves into two groups: (1) the patients with paralumbar psoas abscesses, and (2) those with psoas abscesses pointing at the

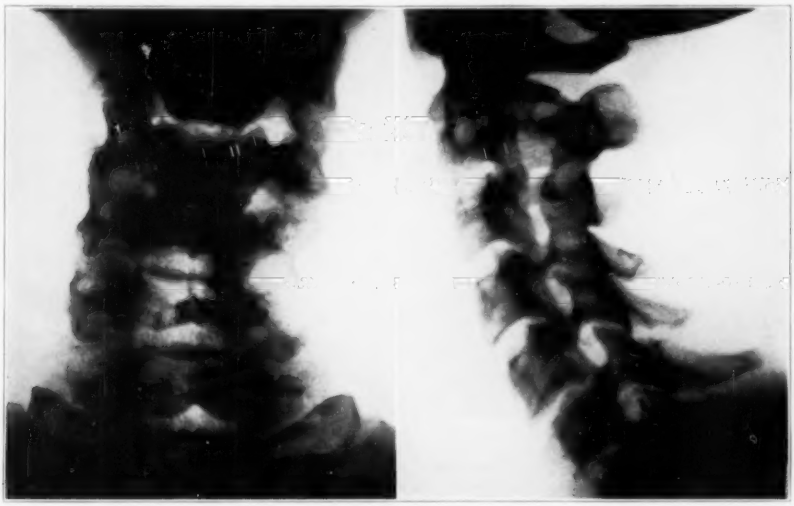

FIG. 13-A FIG. 13-B

Figs. 13-A and 13-B: Case 38, A. H. August 4, 1949. This patient was brought into the emergency room following sudden collapse and complete apnoea due to tracheal obstruction from a tuberculous abscess of the cervical vertebrae. Tracheotomy was performed, and drainage of abscess was done about one week later.

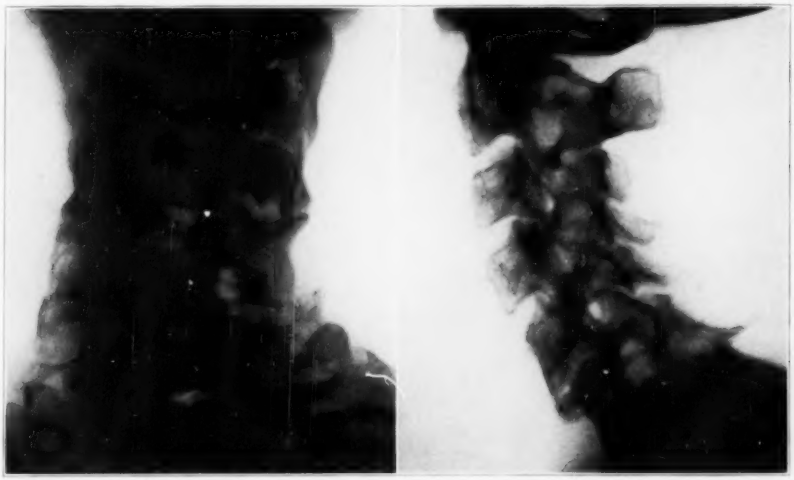

FIG. 13-C FIG. 13-D

Figs. 13-C and 13-D: December 5, 1950. Note the roentgenographic evidence of reestablishment of bony laminal structure. Healing of the neck lesion was uneventful, but tuberculous lesions of the first rib, knee, and shoulder later developed. All were successfully treated.

FIG. 14-A

FIG. 14-B

Figs. 14-A and 14-B: Case 16, M. H. July 24, 1947. Roentgenograms made before the operation showed a large paraspinal abscess. Clinically the lesion progressed despite seven months of complete recumbency. A Hibbs type of spine fusion and drainage of abscess through a separate lateral incision were done at the same operation.

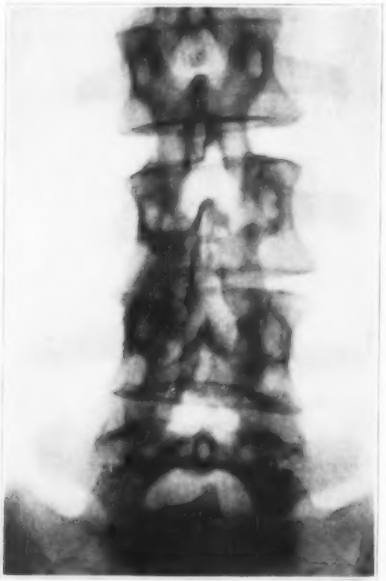

FIG. 14-C

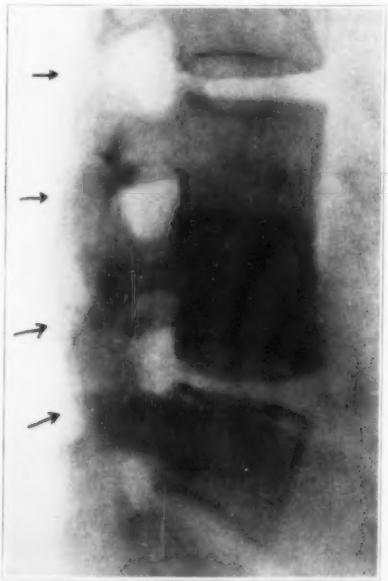

FIG. 14-D

January 3, 1951. The patient became weight-bearing fourteen days after the operation and wore a brace for one year. She was completely asymptomatic when last seen.

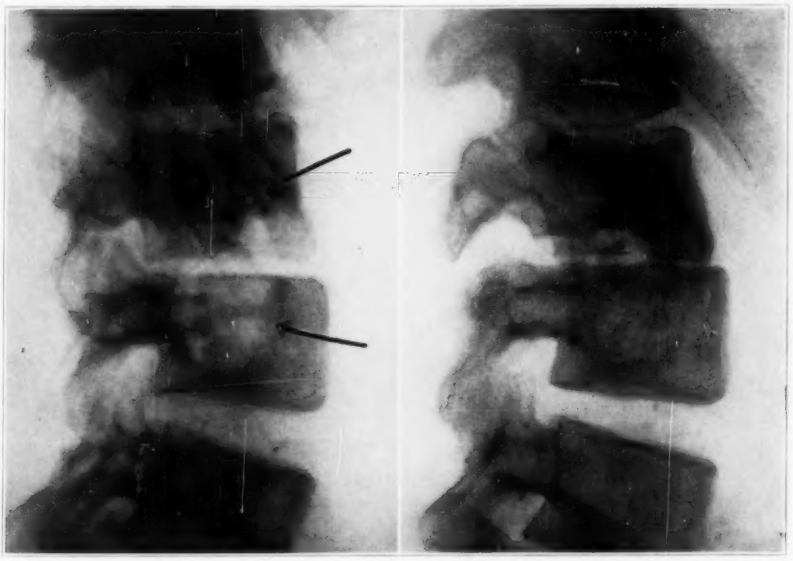

FIG. 15-A FIG. 15-B

Fig. 15-A: Case 49, A. B. January 13, 1950. The patient presented a very large psoas abscess extending from hip to knee, and a large, palpable paralumbar abscess. Both were opened; a rubber drain was inserted in the thigh and gauze packing in the paralumbar approach to the body of the vertebra.

Fig. 15-B: January 12, 1951. The patient became ambulatory on the seventh day after the operation. No immobilization of the spine was used. The sinus closed two months after operation, and unrestricted physical activity was permitted four months after operation.

groin or in the thigh. Although one patient in the latter group was treated by incision in the groin and insertion of packing well up toward the mid-lumbar region with a packing forceps, the remainder were treated by paralumbar approach directly to the involved vertebral bodies. The thigh abscesses were merely incised and rubber drains were inserted to prevent their refilling. The operative approach was by longitudinal incision at the lateral border of the erector spinae muscle group, retraction of the muscle mass medially, detachment of the paralumbar fascia and psoas muscles from the transverse processes, and blunt dissection anteriorly, usually with a gauze-covered finger pressed against the lateral vertebral body. Most often the bulging abscess was opened by the stripping or with scissors and, after evacuation of the pus, the lesion was apparent, since further dissection had already been done by the abscess-sac formation. Spine fusion was done in a few of the earlier cases (Figs. 14-A to 14-D), but was discontinued after it was found that excellent bone regeneration occurred (Figs. 15-A and 15-B), and that in some cases spontaneous fusion of the bodies resulted. The authors do not believe that it is necessary to do a spine fusion to arrest the progress of the tuberculous destruction. It remains to be seen whether arthrodesis may become necessary in some cases because of painful motion or reactivation of the lesion, although this has not yet been encountered in our series. Early ambulation has been allowed, and some form of immobilization was used in most cases, depending on the type and degree of destruction shown in the roentgenogram. It is our opinion that braces or casts are not required beyond six months to one year at most; we have tried even shorter periods, and more recently we have used no immobilization at all.

Spinal Tuberculosis with Paraplegia

Three cases of thoracic-spine involvement with paraplegia were treated by costo-

FIG. 16-A FIG. 16-B

Figs. 16-A and 16-B: Case 39, A. G. September 23, 1949. A decompression laminectomy had been done on August 24, 1949, but the neurological involvement—paraplegia—had become progressively more complete. Costotransversectomy was performed on September 6, 1949, with drainage and packing of the paravertebral abscess in the region of the ninth and tenth thoracic vertebrae.

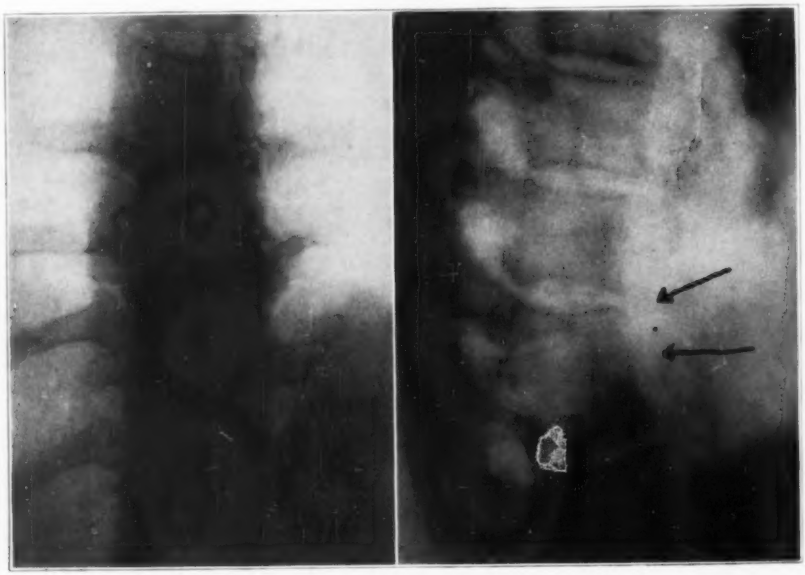

FIG. 16-C FIG. 16-D

Figs. 16-C and 16-D: February 19, 1951. Excellent healing was demonstrated both clinically and by roentgenogram. There was complete recovery from the paraplegia and the sensory loss. No external support had been worn for six months previous to these films.

transversectomy and evacuation of the paraspinal abscess, removal of sequestra which were found to be free in the area of destruction, and the insertion of gauze packing from the vertebral lesion to the skin. No attempt was made to close the skin incisions.

Case 3. J. W., aged eighteen, had had previous lesions in the lumbar area which had been treated in September 1947, and were apparently progressing satisfactorily. There was sudden onset of fever, cough, and chest pain about one year following treatment of the lumbar lesions. Roentgenograms of the chest revealed a large circumscribed density (four centimeters in diameter) in the right upper lobe, resembling a metastatic malignant lesion rather than a tuberculous focus. Toxicity was marked and fluctuation in temperature ranged from 94.4 to 103.8 degrees within a four-hour period. Streptomycin was given for fifty-six days, and general improvement occurred, although there was a daily temperature elevation of 100 to 102 degrees. Three months after onset of the toxic reaction, the patient began to have sensory and motor loss in both lower extremities and the lower torso. This progressed to an almost total involvement, despite complete recumbency for the entire time. Roentgenographic studies showed a destructive lesion of the fourth and fifth lumbar vertebrae, with paraspinal abscess and involvement of the fifth, sixth, and seventh ribs on the right. In December 1948, costotransversectomy was done and, in the course of dissection and removal of the fifth and sixth ribs, a large retropleural abscess was entered, which explained the pulmonary lesion seen on the roentgenogram. The paraspinal abscess was drained and routine treatment was given. The postoperative course was stormy for about one week, after which there was gradual improvement, with rapid return of sensation and much slower return of motor function. The sinuses were closed by March 1949, at which time the patient was walking about in a cast. She was last seen in October 1949, when she was taken to Alabama for the winter. There was evident progression of the pulmonary and kidney tuberculosis, and the patient died of uraemia in July 1950.

The most striking result was that seen in Case 39.

A. G., a white female, fifty-three years old, was admitted with paraplegia secondary to tuberculosis of the ninth thoracic vertebra. When she was seen on August 31, 1949, there was loss of function of the lower extremities, sensory loss, and paralysis of bowel and bladder. Decompression laminectomy had been done one week previously, but the neurological condition became progressively worse (Figs. 16-A and 16-B). On September 6, 1949, a costotransversectomy of the ninth and tenth thoracic vertebrae was done, with drainage of the paraspinal abscess; two days later the patient voided voluntarily, and early functional return of the lower extremities was already evident. Closure of the sinus occurred rapidly—after thirty-six days—but recurrence of a small sinus required a second course of streptomycin (twenty days). At present, there is complete functional return, painless back motion, and roentgenographic evidence of healing with spontaneous fusion (Figs. 16-C and 16-D).

The third case, Case 50, B. H., aged fifty-two, had return of about 50 to 75 per cent. of function of the lower extremities, but because of a far advanced concomitant pulmonary lesion with cavitation, the patient had been at complete bed rest. The sinus of the thoracic vertebrae is well healed and no symptoms are referable to this area, but the prognosis for the pulmonary lesion is very poor.

END RESULTS

The cases with excellent and good results and the criteria for their evaluation follow:

Excellent (Thirty-seven Cases)

1. Cessation of bone and joint destruction.
2. Closure of all sinuses.
3. Absence of pain.
4. Retention of 75 per cent. or more of active peripheral-joint motion or solid surgical fusion when performed.
5. No recurrence of drainage.
6. Improvement in general health.

Good (Thirteen Cases)

1. Cessation of bone and joint destruction.
2. Closure of all sinuses.
3. Relief of pain.
4. Retention of 25 per cent. to 75 per cent. of active peripheral-joint motion.
5. Recurrence of slight drainage, additional streptomycin being required for closure.
6. Improvement in general condition.

TABLE II

SUMMARY OF DATA ON ALL CASES IN THIS SERIES

Case No.	Initials	Age (*Years*)	Sex	Color	Location of Lesion	Date and Type of Operation	Streptomycin (*Days*)	Streptomycin (*Total Amount in Grams*)	End Result
1	W. A.	42	M	W	Ninth and tenth thoracic vertebrae	October 1946: Drainage of paravertebral abscess	27	81	Sinus closed in three weeks. No evidence of activity to present.
2	B. J. C.	16	F	B	Thoracolumbar vertebrae	November 1946: Drainage of abscess	36	72	Second course of streptomycin given 5 months after first course, with closure of sinuses. Healed to present.
3	J. W.	17	F	B	Lumbar vertebrae	February 1947: Incision and drainage of abscess	31	31	Slight occasional drainage.
					Thoracic vertebrae (paralysis)	December 1948: Drainage of paravertebral abscess and resection of tuberculous ribs	112	184	Complete return of function of legs and closure of sinus. Patient died of kidney and lung tuberculosis and uraemia in June 1950. X-rays revealed no progress of bone lesions and apparent healing.
4	J. M.	3½	F	W	Knee	April 1947: Curettage of femur and packing	44	67	Full range of motion and weight-bearing. Normal growth.
5	R. K.	28	F	W	Wrist	April 1947: Incision and drainage and packing	34	34	Full range of painless motion. Roentgenographic evidence of healing.
6	M. F.	34	M	W	Ankle	April 1947: Curettage and drainage	36	36	Sinuses closed. Ankle fusion painless.
7	D. B.	3	M	B	Shoulder	May 1947: Incision and drainage	87	130	Complete healing evident by x-ray. Full painless function.
8	C. H.	8	M	W	Thoracic vertebrae	June 1947: Drainage of abscess and packing	47	47	Sinus healed. Cessation of destruction evident by x-ray. Spontaneous fusion (brace for 2 years).
9	R. S.	28	M	W	Thoracolumbar vertebrae and pelvis	July 1947: Drainage of paravertebral abscess	91	62	Surgical sinus closed in 7 weeks after streptomycin therapy. Pelvic sinuses closed except one when streptomycin and dihydrostreptomycin were stopped because of toxicity. Patient died of amyloid disease and marked kidney tuberculosis with uraemia in August 1950.

(TABLE II—*Continued*)

10	A. H.	38	M	W	Lumbar vertebrae	July 1947: Incision and drainage	68	68	Complete closure of sinuses. Roentgenographic evidence of healing. Full activity without pain.
11	R. R.	2	F	W	Knee	July 1947: Curettage Sequestrectomy and packing	93	93	Complete healing evident clinically and by roentgenogram. Full range of motion.
12	N. H.	32	F	W	Thoracic vertebrae (paralysis)	August 1947: Paravertebral abscess drained	66	66	Mild residual spasticity of lower extremities. Sinus closed and bone healing evident.
13	C. M.	13	F	B	Hip	November 1947: Drainage of pelvic abscess Arthrodesis of hip	76	76	Sinus closed in 7 weeks. Fusion did not occur. Patient has about 35 per cent. of painless hip motion and is fully weight-bearing.
14	L. S.	30	M	B	Ribs, sterno-clavicular, and sacro-iliac-joint	December 1947 and October 1948: Incision and drainage and packing	105 59	157 68	Closure of sinuses. Roentgenographic and clinical evidence of recurrence.
15	T. W.	24	M	B	Left wrist	July 1948: Sequestrectomy	72 47	72 47	Excellent function despite marked roentgenographic evidence of destruction. Recurrence of slight drainage but closure with additional streptomycin.
16	M. H.	38	F	W	Lumbar vertebrae	January 1948: Spine fusion Incision and drainage of paravertebral abscess	26	38½	Sinus closed in 11 days. Rapid solid spine fusion. Asymptomatic.
17	M. S.	22	F	W	Lumbar vertebrae	January 1948: Incision and drainage of paravertebral abscess	47	47	Sinus closed in 30 days. Cast and brace worn for 2 years. X-ray and clinical evidence of healing.
18	W. H.	36	F	W	Right wrist	February 1948: Curettage and packing	88	88	Sinus closed in 18 days. Cast for 3 mos. There was fusion and the patient was asymptomatic.
19	M. V.	11 mos.	F	W	Right knee	April 1948: Curettage and packing	33	33	Rapid healing. Full range of motion and painless weight-bearing.
20	C. S.	44	F	W	Lumbar vertebrae	June 1948: Incision and drainage of paravertebral abscess	15 189	15 189	Sinus of lumbar vertebrae closed but sinuses (old, not operated upon) of ilium and right hip persisted. All closed with long course of streptomycin except one small sinus of the trochanter.

(TABLE II—*Continued*)

Case No.	Initials	Age (*Years*)	Sex	Color	Location of Lesion	Date and Type of Operation	Streptomycin (*Days*)	Streptomycin (*Total Amount in Grams*)	End Result
21	M. W.	52	F	W	Sternum and ribs	June 1948: Curettage and packing	96	96	Complete healing. No recurrence.
22	C. H.	2	M	B	Thoracic vertebrae	July 1948: Incision and drainage	149	149	Healing of sinus in 26 days. No further destruction of vertebrae. Long course of streptomycin for pulmonary lesion.
23	C. H.	50	M	W	Right ankle and subtalar region	August 1948: Arthrodesis	63	63	Diagnosis made postoperatively. Sinuses formed spontaneously. Closure and solid fusion with streptomycin.
24	B. M. K.	48	F	W	Lumbar vertebrae	October 1948: Incision and drainage of psoas abscess	42 (preoperatively) 47 (postoperatively)	42 47	Sinus closed in 8 weeks. Progressive healing evident by x-ray. Brace being worn.
25	N. M.	36	F	W	Left foot	August 1948: Curettage and sequestrectomy	44	44	Painless full weight-bearing with good motion. X-ray evidence of healing. No drainage.
26	A. S.	37	F	W	Right knee	May 1947: Synovectomy	18	18	Streptomycin discontinued because of toxicity. Progressive destruction despite immobilization in a cast.
27	N. L.	39	M	B	Sternocostal area	December 1948: Arthrodesis January 1949: Curettage and packing	90 Dihydrostreptomycin 62	90 93	Dihydrostreptomycin tolerated. Rapid fusion and healing. Clinical evidence of healing. Sinus closed in 6 weeks.
28	L. M.	24	F	B	Left trochanter (?) Ilium (?)	February 1949: Incision and drainage	35	35	Sinus closed in $3\frac{1}{2}$ weeks. Patient is asymptomatic and has full motion.
29	R. K.	34	M	W	Right costosternal region, thoracic vertebrae, and sacroiliac joint	February 1949: Incision and drainage and packing of all lesions	56	56	Sinuses closed in less than 3 months. Roentgenographic and clinical evidence of healing.
30	M. S.	34	M	W	Right sacroiliac joint	February 1949: Curettage and packing	72	72	Closure in 8 weeks. Roentgenographic and clinical evidence of healing.

(TABLE II—*Continued*)

31	D. H.	18	M	W	Left ankle	April 1949: Incision and packing	87	130	Complete closure and full weight-bearing in 4 months. Roentgenographic evidence of healing. Full range of motion.
32	H. T.	72	M	B	Lumbar vertebrae	April 1949: Incision and drainage of paravertebral abscess	66	66	Closure of sinus in 6 weeks. No immobilization. Asymptomatic.
33	W. C.	44	M	B	Thoracolumbar vertebrae	April 1949: Incision and drainage of paravertebral abscess	70	70	Closure of sinus in 6 weeks. Back brace for 1 year. Asymptomatic.
34	B. B.	42	F	W	Left shoulder	April 1949: Incision and drainage	74	74	Sinus closed in 6 weeks. No further bone destruction. 50 per cent. of joint motion.
35	M. W.	38	F	W	Thoracic vertebrae	April 1949: Incision and drainage of paravertebral abscess	74	74	Sinus closed in 7 weeks. Cast for 3 months. Asymptomatic.
36	J. W.	48	F	W	Left hip	April 1949: Sequestrectomy and synovectomy	14	14*	No drainage. Painless full weight-bearing. Range of motion: Flexion, 60 degrees; abduction and adduction, 10 degrees; some rotation.
37	M. C.	28	M	W	Lumbar vertebrae	June 1949: Curettage of sinuses and packing	120	120	Sinuses all closed in 12 weeks. Roentgenographic evidence of healing. Asymptomatic.
38	A. H.	20	M	B	Cervical vertebrae	July 1949: Incision and drainage of abscess	54	54	Closure of sinus in 4 weeks.
							36	36	Opened 4 months later and closed with additional streptomycin. Neck has remained healed.
39	A. G.	53	F	W	Thoracic vertebrae (paralysis)	August 1949: Laminectomy September 1949: Incision and drainage of abscess	94	94	Complete return of function of lower extremities, bladder, and bowel. Sinus closed. Asymptomatic. Brace was worn for 1 year.
40	W. W.	31	M	B	Sternoclavicular region	July 1949: Curettage and packing	62	62	Closure of sinus in 6 weeks. No recurrence.
41	G. C.	28	M	B	Rib	September 1949: Curettage and packing	42	42	Sinus closed in 3 weeks. No recurrence.
42	R. C.	32	M	W	Ilium	March 1948: Resection of ilium	25	25*	All sinuses (12) closed. Full painless weight-bearing. Roentgenographic evidence of healing. Marked gain in weight.

(TABLE II—*Continued*)

Case No.	Initials	Age (*Years*)	Sex	Color	Location of Lesion	Date and Type of Operation	Streptomycin (*Days*)	Streptomycin (*Total Amount in Grams*)	End Result
43	W. S.	21	F	W	Wrist	November 1949: Sequestrectomy and drainage	43	43	Despite deformity, has about 75 per cent. of full motion. No pain. No drainage.
44	E. B.	32	F	B	Thoracic vertebrae	December 1949: Incision and drainage of paravertebral abscess	71	71	Closure of sinus. Cast for 3 months. Brace for 6 months. Asymptomatic.
45	M. S.	2	F	W	Hip	January 1950: Curettage and drainage	66	66	Full range of motion and weight-bearing. X-ray evidence of healing.
46	H. B.	36	M	W	Sacro-iliac joint	February 1950: Curettage and packing	54	54	Closure of sinus in 5 weeks. Asymptomatic. X-ray evidence of healing.
47	B. P.	26	F	B	Sacro-iliac joint	February 1950: Curettage and packing	68	68	Clinical and x-ray evidence of healing. Pregnancy with normal course and delivery January 1951. Condition excellent.
48	M. W.	62	M	W	Elbow	April 1950: Incision and drainage and packing	92	92	Retention of 25 per cent. of motion. Sinus closed. Mild residual pain occasionally.
49	A. B.	25	M	B	Lumbar vertebrae	January 1950: Incision and drainage of paravertebral and psoas abscesses	126	126 (amithiozone 0.5 milligrams three times a day)	Sinuses closed by 11 weeks. X-ray evidence of healing. Asymptomatic. No immobilization.
50	B. H.	52	M	W	Thoracic vertebrae (paralysis)	January 1950: Incision and drainage of paravertebral abscess	86	86	Partial return of function of both lower extremities. Sinus closed in 9 weeks. Patient has far advanced pulmonary tuberculosis.
51	J. D.	17	M	B	Lumbar vertebrae (laminae) Sacro-iliac joint	April 1950: Curettage and packing	72	72	Complete closure of sinuses. Asymptomatic. No immobilization.
52	S. B.	36	F	W	Sacro-iliac joint	May 1950: Curettage and packing	96	96	Complete closure of sinus. No pain with full activity. Clinical and x-ray evidence of healing and fusion.

* Record of dosage after discharge from hospital not available from referring physician.

Deaths (Two Cases)

1. Case 3, J. W., died eighteen months after last operation, of kidney and lung tuberculosis as well as, probably, amyloid disease, although the bone lesions were well controlled and healed or healing.
2. Case 9, R. S., died of amyloid disease and marked kidney destruction thirty-seven months after operation. The bone lesions had appeared to be healing.

COMMENT

This clinical study, representing a radical departure from the accepted method of treatment of tuberculous bone and joint lesions, was presented as a scientific exhibit at the Annual Meeting of The American Academy of Orthopaedic Surgeons in January 1951. At that time the authors were asked many questions, and those who attended the meeting expressed a variety of opinions. We agree that any procedure so diametrically opposed to principles of treatment which have been taught for so many years cannot be accepted on the basis of a series as small as this. Moreover, the follow-up period, although it averages over three and one-half years after operation, must be considered short in a chronic and recurrent condition like tuberculosis. We are, therefore, presenting this study as a preliminary report and expect to continue the observation of the patients of this series, and those treated in the past two years and in the future, in order to answer the question which is foremost: "Will this condition in these patients continue to remain arrested or healed?"

Arthrodesis

Many expressed the opinion that an excellent opportunity of obtaining fusion of these joints was being missed by not performing an arthrodesis during the period when there was clinical and roentgenographic evidence of arrest or quiescence, and that the only permanent cure was one in which an arthrodesis was obtained. It is our feeling that, in children, the gain of normal growth in the extremities outweighs the risk of reactivation of the lesion. We believe that, if there is recurrence, repeating the procedure should be as effective as the initial procedure, particularly if there is frequent follow-up observation so that recurrence may be diagnosed in early stages. So far, there have been no recurrences, and we do not know the answer to this problem, nor do we know whether surgical fusion would be performed if reactivation occurred. However, with each passing year, we can hope for more knowledge, more effective antibiotics, and improvement in technical procedures, which should favor the patient's eventual end result. In the single case in which autopsy was performed—thirty-seven months after surgery—there was no gross or histological evidence of a tuberculous lesion in the previously involved and treated segments of the thoracic spine.

Effect of Streptomycin Alone in Lesions without Sinuses

A number of the patients in this series had been given streptomycin for prolonged periods in the treatment of concomitant pulmonary lesions. Despite this, bone and joint lesions developed and progressed. Moreover, in a few of the cases second and third lesions involving other areas of the body developed, while the primary, treated lesion was healing or after it had healed. Other authors [1, 10] have expressed skepticism of the ability of streptomycin alone to heal a bone or joint lesion permanently, and their experience has coincided with our observations in this series. Although there is general agreement that it serves prophylactically against sinus formation, enables surgical procedures to be done safely in the presence of sinuses, and is immeasurably effective in any attack directed primarily against the sinuses themselves, there is little to be found in the literature generally as to its effectiveness against the progressive closed lesion.

Streptomycin Resistance of the Organism

No definitive studies have been conducted in this series, nor have we been impressed that the factor of development of resistance to streptomycin has been of any consequence. The period of administration of streptomycin was frequently affected by treatment of coexisting pulmonary lesions; some patients were given continuous dosage of streptomycin for six months or more. Despite this variation in length of time, we have seen no case in which the sinus ceased in its healing process as long as streptomycin was administered continuously. In a few cases, when streptomycin was discontinued before the sinus was closed, the sinus showed no tendency to continue healing. But when administration of streptomycin was resumed, healing also resumed.

Metastatic Lesions

In two patients additional lesions developed eleven months and twenty-two months following operation of the initial bone and joint lesions. There were three patients who presented multiple lesions when first seen. No evidence has been observed to confirm the impression that surgical intervention may produce metastases.

Primary Closure

Although none of the patients in this series were treated by primary closure rather than packing open the sinus, we realize that many surgeons have used this variation from our procedure. From personal conversation with some of these men, it was learned that a large percentage of lesions so treated apparently remain closed and progress satisfactorily. The procedure is too recent to evaluate, because of the generally short period of follow-up. Also, in a number of patients so treated draining sinuses tend to form after apparently good initial healing, and it is our impression that in these sinuses spontaneous closure is slower compared to those produced by gauze packing.

Future observation may show some advantage to primary closure, but only the study of more cases, with longer periods of follow-up, can decide the controversy. The method would certainly have definite advantages if it is shown to be as successful.

It is hoped that future research may give us a more potent agent than streptomycin, para-animosalicylic acid, and the other drugs now being used which may eventually obviate the necessity of surgical intervention in any form. However, just as penicillin and the host of other effective antibiotics still have not led to abolishment of the surgical principle of adequate drainage in the pyogenic group of suppurative infections, so streptomycin has failed to obviate the necessity for surgery in tuberculous bone and joint infections.

CONCLUSIONS

1. Following adequate surgical drainage and streptomycin therapy, destruction from bone and joint tuberculosis has been found to cease, and roentgenograms showed evidence of recalcification and apparent regeneration of bone. There has been no tendency toward reactivation of the lesion, clinically or symptomatically.

2. In closed bone lesions, the use of streptomycin alone has failed to control the progress of the disease in most cases.

3. In the surgically produced sinuses, subsidance of drainage and closure in periods of time varying from three to sixteen weeks has invariably taken place.

4. Although the surgically treated lesions will heal clinically, new lesions in other parts of the body may develop and progress, despite administration of streptomycin.

5. While lesions adequately drained surgically are healing, pre-existing sinuses from other lesions may fail to close.

6. The tendency for bone regeneration to occur in children, with re-establishment

of an apparently normal epiphyseal plate and no disturbance in the rate of growth, has been particularly evident and gratifying.

7. A good functional range of motion in peripheral joints has been retained in almost all cases, with little or no residual pain.

8. In those few cases in which a surgical arthrodesis was performed, fusion tended to occur rapidly.

9. A good functional range of motion has been the usual end result, even when there was roentgenographic evidence of extensive destruction of the joint.

10. The factor of secondary infection has apparently been of no consequence in the arrest and healing of these lesions.

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DISCUSSION

Evaluation of Streptomycin Therapy

(*Continued from page 298*)

years of its use. One was the idea which had been advanced that in practically all cases the organism became resistant to streptomycin. I don't know what the statistics are that led to that conclusion. I have been interested to note that the speakers have disregarded that possibility, and I think we should do so.

The other reason for discontinuing the antibiotic too early was that in the first cases we used larger doses of streptomycin, probably larger than we needed to. With smaller effective doses, we can continue it for a longer period of time without toxicity except in very few cases.

It has been our impression, and I think that of the other speakers as well, that the cases in which streptomycin is most effective are those acute cases where the disease is very active. The sedimentation rate is high, the disease is progressing, and the patient is toxic. Those patients have almost always responded very dramatically to the use of streptomycin. I doubt whether in old cases, in which the disease is quite inactive, the sedimentation rate is low, and a damaged joint requires arthrodesis, the use of streptomycin is worth while or even advisable. We know that in the past the results from operative treatment in such cases were very good without streptomycin, and I still think they remain so. I think we may find that there are a few cases in that group where the use of streptomycin is inadvisable.

There is no question that the treatment of tuberculous abscesses has been revolutionized by the use of

streptomycin. We used to avoid in every way possible the opening of an abscess, fearing secondary infection and long drainage, but now in the case of a large abscess we do not hesitate to incise and drain the abscess and use streptomycin; we find that such an abscess usually closes, and that the patient is much improved in a much shorter period of time.

There were three patients with synovial tuberculosis of the knee joint whom we attempted to treat by synovectomy, as complete as possible, combined with the use of streptomycin. I would like to report that in two of these cases the method was an absolute failure. We failed to control the disease and we had to arthrodese the joint. In the third child, in whom the upper pole of the patella was involved, this also was excised. The disease, as far as we can tell, is still inactive, although I think the patient will have to be followed for many years before we know whether or not the disease will recur. Cases have been reported of the subsidence of synovial tuberculosis of the knee after use of streptomycin alone. That may be one form of joint tuberculosis in which streptomycin will be effective. Certainly fusion of the knee is most crippling, and I think that, if it is possible to avoid arthrodesing the knee joint, it will be very much worth while.

We are observing with great interest several patients with tuberculous meningitis who have other lesions, — one of a hip and two of the spine. It seems inadvisable to operate on these patients at the present time although the spinal meningitis seems to be under control. We were afraid we might reactivate it by operating and by using an anaesthetic. In one of these a very active tuberculosis of the spine shows quite a remarkable subsidence after treatment with streptomycin alone. Fusion may be required in this case, but it is interesting to observe the effect of streptomycin without surgery. These are the only patients whom we have attempted to treat with streptomycin in this way.

Dr. J. Albert Key, St. Louis, Missouri: I would like to reiterate what Dr. Evans says about being radical. I regard tuberculosis somewhat as I do a malignant disease and I attempt excision of all diseased tissue. I consider streptomycin as a useful adjunct, but not a substitute for surgery.

In line with the question of cure by streptomycin, we had one case recently with knee involvement in which we had fused a wrist about two years ago and then fused the spine; at the time of the first fusion there was a little fluid in the knee. Streptomycin was given in the knee and systemically for quite a long time. Recently the patient came back with tuberculosis of the knee. Two years ago fluid from the knee was negative for tuberculosis.

I would like to mention tuberculosis in areas that lie in the border zone between orthopaedic and general surgery. These include tuberculosis of the tendon sheath (especially at the wrist), of the fascia (especially of the back), of bursae (especially over the greater trochanter), of the sternum, the sternoclavicular joint, and the pubic synchondrosis. In all of these, I believe in radical excision of the diseased tissue except the tendons. The bone is expendable. I have excised the pubis widely, for instance, in two patients, removed wide sections of the sternum in three patients, and have resected a lot of clavicle and sternum at the sternoclavicular joint. In disease of the trochanter, I have excised the bone widely with the overlying bursa and abscess.

Our patients do not have custodial care. They have to get out and make a living. We cannot keep them in the hospital over long periods and have somebody support them. We have to cure them as quickly as possible. It is a matter of weeks with us, not months and years. By means of radical excision, one can usually cure the disease in the above mentioned areas fairly promptly with or without streptomycin.

Dr. Bosworth (closing): In closing I want to thank Dr. Howard Wright, Dr. William Fielding, and Dr. Raymond Goodrich for assistance in compiling material and statistics for my portion of this Symposium.

In the cases reported by us there has been personal contact with the patients throughout prolonged periods of hospitalization at Sea View Hospital and following discharge from that institution for longer follow-up periods at St. Luke's. No cases have been lost.

The City of New York has provided us not only with the housing and other facilities for the care of these patients for prolonged study, but also with the streptomycin and any other medication or apparatus we cared to use. One might call them "kept patients" of the City of New York.

The answer to the question of complete healing of synovial lesions, or the possibility of arthroplasty of an ankylosed tuberculous joint following prolonged periods of streptomycin will have to await the future. Assumption that healing is complete or that the disease in such reconstructed joints will not recur is extremely questionable with our present knowledge. We would feel that arthroplasty of an ankylosed tuberculous joint should not be done.

Conclusions reached in our paper read in January 1949 [a] though greatly questioned at that time, appear amply substantiated by all authors contributing to this Symposium.

Para-aminosalicylic acid, tibione, and other adjuvants of that kind have been repeatedly shown to be ineffective in tuberculosis when used alone. For that reason I see no necessity of combining them with streptomycin. To add one further drug carries with it the possibility of resultant toxicity. Future statistics of others will finally decide this point.

a. Bosworth, D. M.; Della Pietra, A.; and Farrell, R. F.: Streptomycin in Tuberculous Bone and Joint Lesions with Mixed Infection and Sinuses. J. Bone and Joint Surg., **32-A**: 103–108, Jan. 1950.

TEAR OF THE SACROSPINOUS AND SACROTUBEROUS LIGAMENTS

BY MICHAEL BURMAN, M.D., NEW YORK, N. Y.

The sacrotuberous and sacrospinous ligaments are torn by direct, and sometimes violent, injury to the sacrum; the lumbosacral joints may be indirectly strained when the lower half of the sacrum is tilted back. The ligamentous tear is made certain only by the avulsion of bone. Tear of the sacrospinous ligament may be accompanied by a fracture of the ischial spine or a fracture *en bloc* of the lower lateral part of the sacrum or both; tear of the sacrotuberous ligament may be accompanied by a similar fracture of the sacrum and a presumptive avulsion fracture of the tuberosity of the ischium and the posterior inferior iliac spine (presumptive only, because they have not been seen). Being more vulnerable, the sacrum breaks; the fracture occurs through the third or fourth sacral foramina or both. (The first and second sacral foramina lie in the lee of the iliac wing.) The attempt should be made to dissociate sprain of the sacrospinous ligament from sprain of the sacrotuberous ligament; however the two sprains probably coexist.

Tear of the Sacrotuberous Ligament

Twelve cases have been seen.

A presumptive diagnosis of tear of the sacrotuberous ligament, lacking the avulsion effect, is justified when the origin and insertion of the ligament are painful and tender by both external and rectal palpation. The patient cannot sit comfortably on the painful ischial tuberosity. If fracture takes place, its site is more likely to be the inferior ramus of the ischium rather than the ischial tuberosity itself, as a fracture through a waist of bone. The continuity of the sacrotuberous ligament with the biceps femoris tendon [5] may result in detachment of a small fragment of bone from the inferior and lateral part of the ischial tuberosity, or may provoke calcification in the tendinous origin of the biceps femoris.

Four of the twelve patients had sciatica, the intensity of which in two was temporarily lessened by the injection of procaine into the tender sacral origin of the ligament. The sciatica in three seemed to follow root pressure by a herniation of disc substance at the lumbosacral level. (This was proved at operation in one case.) The partial relief of sciatic pain by the injection of procaine into the ligament and the induction of such pain in one of the patients when one point in the ligament was touched with the needle indicated that the sciatica was caused reflexly by irritation of the ligament and directly by pressure on a nerve root. Heyman stripped the glutaeus maximus and the posterior superior and inferior iliac spines in two cases, which resulted in the relief of sciatica. It is likely that the iliac origin of the sacrotuberous ligament was also stripped.

Fracture of the Ischial Tuberosity

An isolated fracture of the ischial tuberosity is rare. There are three possible forms of fracture.

Berry reported the first case of avulsion fracture of the ischial tuberosity in the English-language literature in 1912; Milch reported the second in 1926. Other cases were reported by H. H. Cohen, Labuz, McMaster, and Abbate. The epiphysis of the tuberosity appears at puberty and unites between twenty and twenty-five years of age. The avulsed epiphysis may be pulled away by the hamstring muscles if the flexed pelvis is fixed, or by sudden flexion of the pelvis if the lower extremity, with the knee extended, is fixed. McMaster described epiphysitis of such an avulsed fragment. Even if the avulsed fragment fails to unite, the result of conservative treatment is usually good.

Fracture of the body of the ischial tuberosity in the adult is illustrated by Key and Conwell who attributed the fracture to a fall in the sitting position. Intra-pelvic avulsion

FIG. 1

Roentgenograms made July 10, 1950, nine months after injury. The inferior ramus of the left ischium shows a healed longitudinal fracture adjacent to the ischial tuberosity. The displacement of the fragments has narrowed the obturator foramen and so distorted it that it lies in a semisagittal plane.

of the upper part of the ischial tuberosity by pull of the sacrotuberous ligament has not been reported.

Multiple Injuries after a Fall, Among Which Is Included Strain of the Sacrotuberous Ligament

CASE 1. A woman, fifty-four years old, fell down fifteen steps on March 19, 1950. She sustained many injuries which included cerebral concussion with unconsciousness, strain of the cervical spine, strain of both

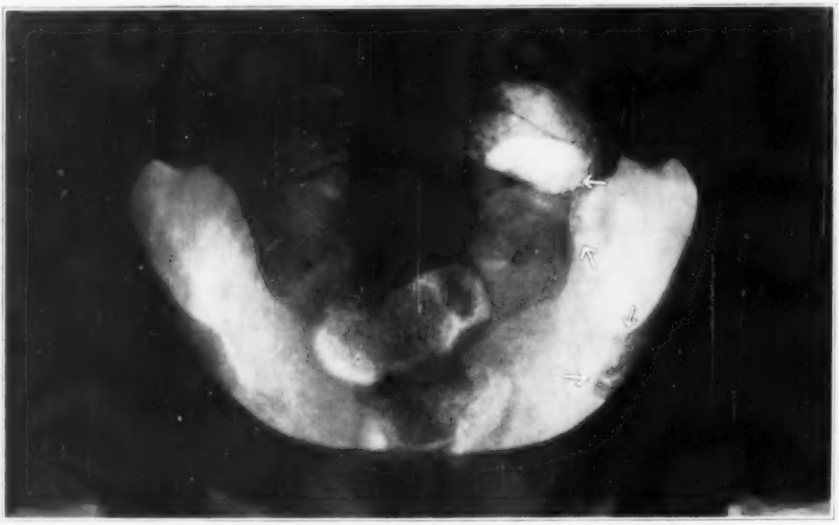

FIG. 2-A

A man, forty-seven years old, was injured on March 21, 1946, when the small truck he was driving was struck from behind by a passenger car. There was a fracture *en bloc* of the lower left lateral border of the sacrum, with a slight tilting of the fragment. The fracture began at the third sacral foramen and ended at the juncture of the sacrum with the coccyx. (Reproduced by permission from the *Bulletin of the Hospital for Joint Diseases.*)

FIG. 2-B

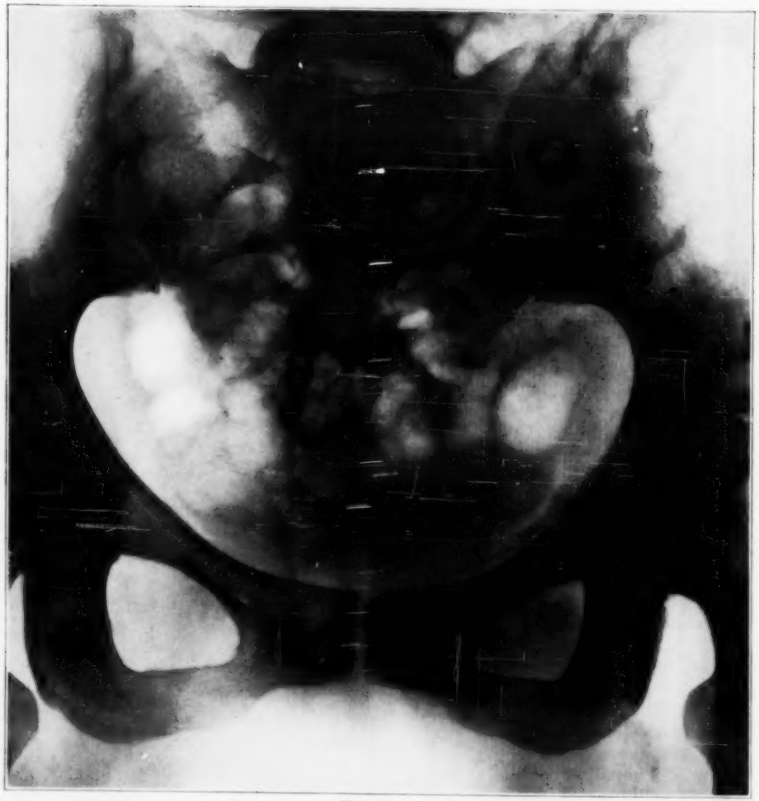

FIG. 3

Fig. 2-B: Comminuted linear fracture of the left ischial spine. (Reproduced by permission from the *Bulletin of the Hospital for Joint Diseases.*)
Fig. 3: Fracture *en bloc* of the lower left lateral part of the sacrum with *distal* rotation and right lateral displacement of the fragment. The fourth sacral foramen is the upper limit of break, the coccyx the lower limit.

shoulders and hips, xiphodalgia, and diffuse strain of the spine. Most of the tenderness overlay the sacrum, especially at its lower lateral borders. Each ischial tuberosity was tender. The coccyx was forwardly angulated and quite mobile. Straight-leg raising on each side was restricted to an angle of 140 degrees. All movements of the spine were greatly lessened and were done painfully and slowly. Ecchymoses were found on the outer side of the left thigh and over the left portion of the low back and hip. She walked with a limp on the left side. Roentgenograms of the pelvis were negative.

Strain of the Sacrotuberous Ligament and Fracture of the Inferior Ramus of the Ischium

Case 2. A man, thirty years old, pulling a loaded hand truck on a busy street, was struck by the bow of the truck in the lumbar region of the back and thrown to the ground when a bus hit the hand truck. Persistent low-back pain, continuing even nine months after the accident, followed a diffuse sprain of the lumbar spine with a fracture of the inferior articular process of the fifth lumbar vertebra. In addition, he also strained the left sacrotuberous ligament. This strain was recognized by the typical sites of tenderness over the lower sacral origin of the ligament and its insertion on the ischial tuberosity. He could not sit on the left buttock. The roentgenogram (Fig. 1) of the pelvis, made on July 10, 1950, revealed a healed longitudinal fracture of the inferior ramus of the left ischium, adjacent to the ischial tuberosity. The displacement of the fragments narrowed and distorted the obturator foramen. There was a lesser strain of the right sacrotuberous ligament.

He was partly relieved of his discomfort by physical therapy and the support given by a belt.

Tear of the Sacrospinous Ligament

The tear of the sacrospinous ligament is certain only when there is avulsion of its origin on the sacrum or at its insertion on the ischial spine. Such a case has previously been reported.[10] Roentgenograms of this case are shown as Figures 2-A and 2-B. Three other cases have been seen. The injury is presumptively recognized by pain and tenderness along the course of the ligament.

Fracture of the Lower Border of the Sacrum Through the Fourth Sacral Foramen with Distal Rotation of the Fragment

Case 3. On August 25, 1948, a woman stopped her car to make a turn on a highway. Another automobile struck her car from behind with such force that her car was moved forty feet over an embankment into a field. She was thrown against the steering wheel and then back into her seat; she was dazed but not unconscious. The many injuries she sustained included cerebral concussion, strain of the neck and spine, and contusion of the xiphoid process.

Fig. 4

Non-union of the avulsed ischial spine and the distally rotated fragment of the sacrum noted in the roentgenogram of October 18, 1949.

She was still extremely nervous on February 9, 1950. She had pain in her back which sometimes was so gripping that she could not talk. She could not stand or sit comfortably. She had been constipated since the accident and had bowel movements only every three to four days, unless she took a laxative. Her sexual desire, never too great, was lessened.

The lower left lateral border of the sacrum was very tender, by both external and rectal palpation. The third sacral foramen could be felt. The sacrum below this was rough and very tender; the coccyx was not tender. A vague bony mass was felt in the left buttock near the lateral edge of the lowermost part of the sacrum. The tone of the rectal sphincter was good, and the rectal mucosa did not prolapse on straining. There were no sensory changes.

The roentgenograms of the spine were negative. The roentgenograms of the sacrum in the anteroposterior and left oblique views were taken after the administration of prostigmine and an enema which were given to dispel the gas obscuring bony detail (Fig. 3). A small, roughly rectangular piece of bone had been broken away from the sacrum, the upper limit of the break being the fourth sacral foramen, the lower limit, the lowermost part of the sacrum near the coccyx. The fragment was rotated distally, the center of moment being the lower level of the fracture, and was displaced to the right. The ischial spine had not broken.

Combined Fracture of the Sacrum and Ischial Spine. Distal Rotation of a Sacral Fragment and Non-Union of the Ischial Spine

Case 4. A man, forty-eight years old, who was about to enter a subway car on April 9, 1948, had his right arm fixed near the shoulder by the sudden closing of the car door. The train dragged him thirty or more feet on the platform of the station before he pulled himself free. He was then thrown to the tracks. He was unconscious for several hours.

He had pain in his back and left hip on July 9, 1948. He could not sit comfortably; he walked five to six blocks slowly; he passed water with difficulty; and he had other complaints resulting from injuries not

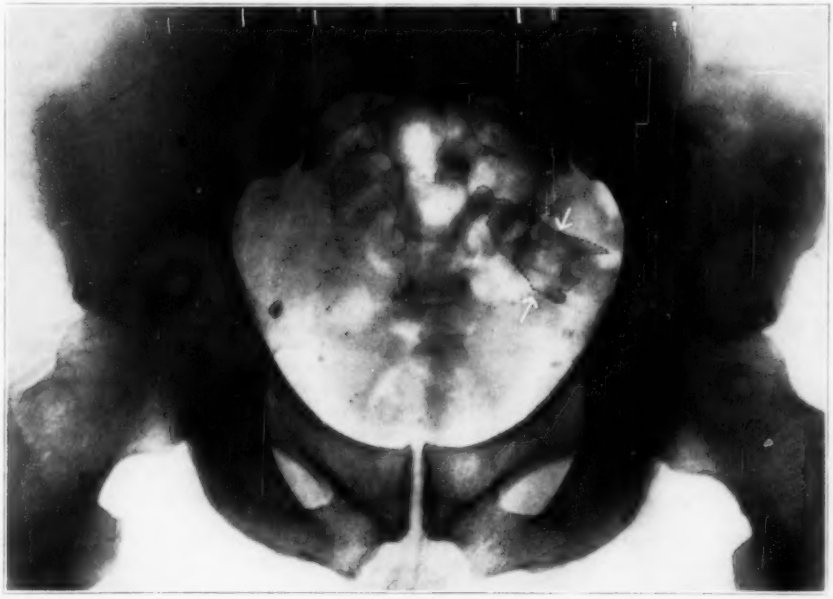

Fig. 5-A

Avulsion of a large sacral fragment with proximal rotation through an arc of 60 degrees.

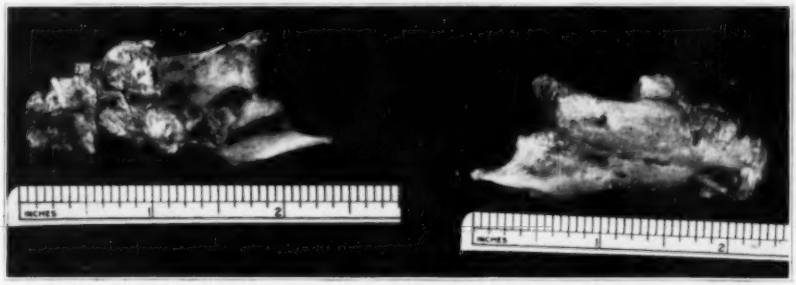

Fig. 5-B

Photograph of the excised fragment of bone.

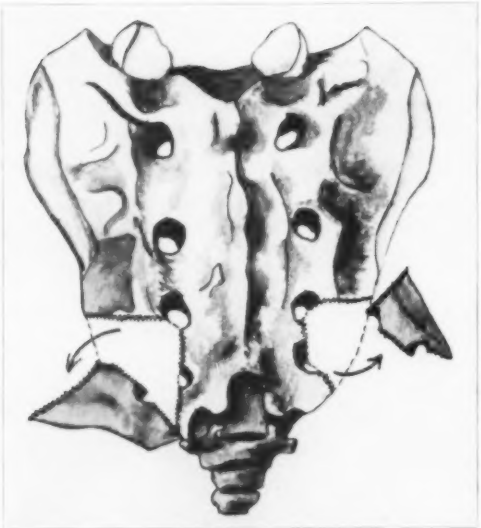

FIG. 6

Diagram illustrating the proximal rotation of the avulsed fragment of the sacrum on the right, the distal rotation on the left. The rotation is made in the plane of the figure, but more complex rotation in the two planes perpendicular to this plane is feasible. The translation of the fragment, equally possible, is not shown. The center of moment in proximal rotation is taken as the mid-part of the third sacral foramen; that of distal rotation, the lowest lateral part of the sacrum.

pertinent to the subject of this article, especially injuries of the head and neck.

The lumbar spine showed a right scoliosis which increased on forward bending, a motion so greatly restricted that the tips of the fingers came only within twenty-four inches of the floor. Extension of the spine was painful and about a quarter of the normal; lateral bending was carried out through half the normal range. Straight-leg raising on each side was possible to 140 degrees. The left, lower, and lateral half of the sacrum was very tender. The region of each ischial spine was very tender. In addition, he had a fracture of the eleventh thoracic vertebra and traumatic synovitis of both hips which limited motion. A healed laceration of the urethra had resulted in stricture.

Roentgenograms revealed the left obturator foramen narrowed by fracture of both rami of the left pubic bone, with moderate displacement of the broken parts. An irregular fracture of the superior ramus of the right pubic bone was found. The left ischial spine was avulsed in association with a fracture *en bloc* of the left lower and lateral part of the sacrum. A fragment of the lowermost part of the sacrum was rotated distally. The lumbar spine was bent and turned to the right; the lumbosacral disc was narrowed. The apophyseal joints of the fifth lumbar vertebra were narrowed and were tilted anteriorly.

He still had pain in his left buttock on October 18, 1949. Flexion of the spine was possible to 100 degrees. When he bent forward, the finger tips came to within ten inches of the floor. Extension and lateral bending were considerably restricted. Straight-leg raising was possible to 110 degrees on the right and to 120 degrees on the left. The left buttock was tender and so too was the lower left border of the sacrum and coccyx. Roentgenograms disclosed a non-union of the avulsed fragments of the ischial spine and sacrum (Fig. 4). His condition was unchanged on March 4, 1952.

Avulsion and Rotation of the Sacral Fragment. The Adjunct Injuries of Piriformis Tear. Rectal Prolapse and Tear of the Sacral Nerve Roots. Operative Resection of the Fragment

CASE 5. A man, forty-five years of age, fell five feet from the tail-board of his truck to the concrete pavement on November 12, 1946. He landed on his buttocks, more on the left than on the right, and then fell back. He bled from the rectum for two weeks. He was thereafter constipated and could not have bowel movements without the aid of laxatives. Sometimes the rectum protruded on bowel movement and he sometimes passed blood through the rectum. He had felt a lump in his left buttock ever since the accident. He became impotent in March 1947. He also had a lumbosacral strain.

A sacral fracture was not discovered until December 10, 1948. At that time he held his left hip stiff and walked with it in abduction. He did not bear weight well on this hip and the Trendelenburg sign was positive. He could not sit on the left buttock. A tender, bony mass with little mobility was felt at the lower left edge of the sacrum under the substance of the glutaeus maximus. On rectal examination, a very tender sacral defect could be felt on the left side. Motions of the left hip were slightly restricted. The left side of the penis and scrotum was numb, but the value of this observation was discounted by the general hypaesthesia on the left side of the body (conversion hysteria). A roentgenogram of the pelvis (Fig. 5-A) disclosed avulsion of a large, irregular, triangular piece of bone from the left, lower, and lateral part of the sacrum. The fragment was rotated proximally through an arc of 60 degrees.

Urological examination (by Dr. J. H. Friedman) was negative except for the complaint of impotence. The proctologist (Dr. Irving Kalow) found prolapse of the rectum and internal hemorrhoids. The great loss of tone of the anal sphincter and the rectal prolapse seemed neurogenic in origin, the result of damage to the nerve supply of the rectum incurred at the time of accident.

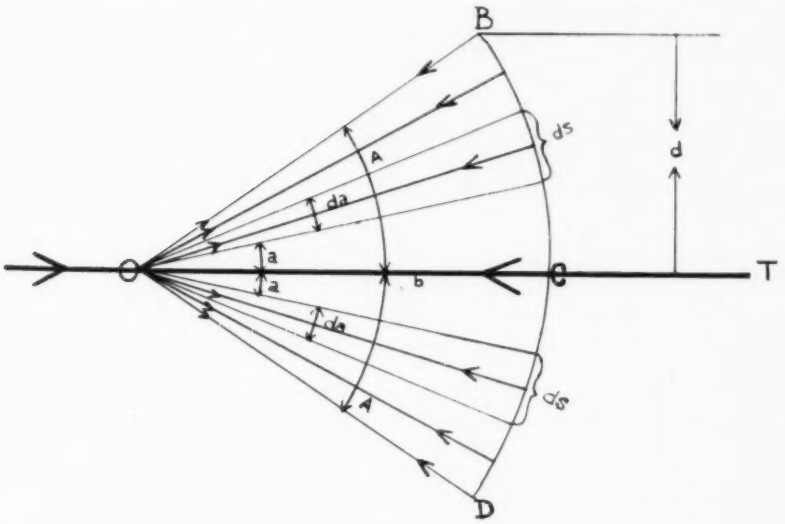

FIG. 7

ODB is a sector of a circle, divided by *OC* into two equal parts. The distributed tension force is replaced by a single resultant force, *T*, located on the radial bisector. Two elements of the circumference of the sector, symmetrically placed with reference to *OC*, are chosen. Each has a length, *ds*, equal to *bda*, where *b* is the length of the radius of the circle and *da* is the differential angle. The magnitude of the force acting on each of these elements is *tbda*, where *t* is the intensity of the distributed tension force on any point of the line *DB*. Each element of force is replaced by its horizontal and vertical components. The vertical components are equal and oppositely directed to cancel each other. Horizontal components summate each other, and their resultant equals $2tb \cos a\ da$ acting through the concurrent point *O*. The total resultant, *T*, is the sum of these elemental resultants from *O* radians through *A* radians.

$$T = 2tb \int_{O}^{A} \cos a\ da$$
$$= 2tb \sin A$$

The moment is $2tbd \sin A$, where *d* is the moment arm. The total moment is the sum of the moments of the two ligaments.

The sacral fragment was excised on May 7, 1949 (Fig. 5-B). The patient was placed in a jack-knifed prone position with the body tilted to the left. The incision was made along the crest of the ilium to the posterior superior iliac spine where it curved distally along the left lateral border of the sacrum and coccyx. The glutaeus maximus was dissected from the sacrum distally and laterally. This exposed the edge of the sacrum and the sacral fragment. The roughly rectangular fragment measured 3.75 centimeters in its long transverse diameter and 2.54 centimeters in the shorter vertical diameter. It had been torn away from the sacrum and had been rotated proximally through an arc of 60 degrees by the tension of the sacrotuberous and sacrospinous ligaments. The center of motion (or of moment) was the proximal point of fracture through the third sacral foramen. The lateral edge of the fragment was scalloped into two indentations and three sharp edges as shown by roentgenograms. The sacral origin of the fragment was filled with fibrous tissue. In the slow and difficult dissection of the fragment, the torn distal part of the scarred sacral nerve root which passed through this foramen was found on the under side of the fragment in the half circle of the foramen. The short stump of the proximal part of the root was seen in the fixed medial part of the sacral foramen. Suture of the nerve root was impossible. The torn piriformis muscle was re-attached to the edge of the sacrum. The internal pudendal nerve was not explored since it lay outside the radius of the circle described by the sacral fragment. The postoperative course was uneventful and the patient left the hospital four days later. The wound healed well. The roentgenogram of June 1, 1949, disclosed a smooth-edged sacrum; the removal of the avulsed fragment was complete.

The left buttock was not tender on October 14, 1949. He could not, however, sit comfortably and he was still constipated; he walked well. A new injury to the left hip on July 5, 1949, provoked a slight limp on the left side, which had almost disappeared by October 14, 1949.

His emotional attitude towards his many complaints (conversion hysteria) remained unchanged in

January 1952. He was still impotent and constipated. Sometimes he still could not sit comfortably on the left buttock, and sometimes he still walked with a limp on the left side. The operative area was not tender and the sacral defect was smooth.

COMMENT

The most obvious expression of combined injury of the sacrotuberous and sacrospinous ligaments is the fracture of the sacrum *en bloc*, to which the ligaments are attached. The small and elastic coccyx does not break, for it is a small target with "give".

In two cases, the ischial spine broke by selective tear of the sacrospinous ligament. The selective strain of the sacrotuberous ligament is most likely to break the inferior ramus of the ischium rather than the ischial tuberosity. Such a fracture was found twice in twelve cases of selective strain of this ligament.

There are three adjunct injuries: contusion or tear of the sacral nerve roots, tear of the piriformis muscle, and rectal prolapse. These are found only in the severest form of this type of injury.

Associated injuries in this series included pelvic fracture, laceration of the urethra, and low-back strain; distant injuries included fracture of a cervical vertebra, fracture of a thoracic vertebra, and head injury.

Strain of the ligaments, without avulsion, may heal quickly or slowly. The undisplaced sacral fracture heals, but the displaced fragment may have to be excised. The avulsed ischial spine, like other tension fractures, may not unite.

The fragment resulting from fracture through the third sacral foramen is considerably larger than the fragment from fracture through the fourth sacral foramen. Ligamentous tension may avulse the sacral fragment, rotate it, and then displace it, only when the fragment is free at each end. The center of motion is either the upper or the lower point of sacral fracture. If it is the upper point, the fragment rotates proximally through an arc of a circle which is unlikely to exceed 90 degrees. Distal rotation of the fragment with a distally placed center of motion also occurs (Fig. 6). The internal pudendal nerve cannot be injured if it lies outside the circle of which the radius is the length of the broken fragment of the sacrum.

THE CALCULATION OF THE MOMENT

The rotation of the sacral fragment may be analyzed mechanically as a problem in distributed force in a plane.[11]

A tension diagram (Fig. 7) is made, comparable to a load diagram. Either ligament is idealized as a sector of a circle. (The sacrospinous ligament is chosen as the example.) The divergent tension forces pulling the ischial spine to the sacrum are equal and opposite to the concurrent tension forces pulling the sacrum to the ischial spine to give equilibrium. The resultant of forces passes through the centroid of the sector which lies along its bisector. In equilibrium the resultant of the concurrent forces equals the resultant of the divergent forces. Each is represented by T (for tension), but with opposite sign. The problem is solved for the resultant of the concurrent forces.

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PARA-ARTICULAR CALCIFICATION AND OSSIFICATION FOLLOWING ACUTE ANTERIOR POLIOMYELITIS IN AN ADULT *

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Para-articular calcification developing after lesions of the spinal cord and cauda equina have been reported in the continental literature on several occasions and occasionally in the English literature. Weir Mitchell, Morehouse, and Keen [2] reported a case following a compression fracture of the twelfth thoracic vertebra. Para-articular calcification following anterior poliomyelitis has been reported on only one previous occasion—by Gustav Drehmann in 1927. In that instance, a boy two and one-half years old became ill with acute anterior poliomyelitis. Approximately six to eight weeks later swelling and pain developed about the left hip joint, resulting in complete stiffness. Roentgenograms showed ossification in the region of the glutaeus medius and the adductor magnus or pectinaeus. The ossification remained completely unchanged, while the paralysis abated. The roentgenograms showed, furthermore, that the hip joint itself was not involved. The original article reporting this case in a Czechoslovakian journal was not available to the author, the foregoing information being obtained from an abstract in the *Zentralblatt für die Gesamte Neurologie und Psychiatrie*. As in all of the later instances of para-articular calcification reported in the literature, the lesions were confined primarily to the areas of the hip joints and to the knees. No case has been described in which the metacarpophalangeal joints or the shoulder joints were involved by these unusual lesions.

André Ceillier, in 1920, in a thesis of 275 pages on what he called para-osteo-arthropathies in paraplegias from lesions of the spinal cord and cauda equina, reported 160 cases, seventy-nine of these, or 49.37 per cent., demonstrating para-articular calcification. In seventy-seven cases in this series the paraplegia was secondary to a traumatic spinal lesion. Of the other two, one was due to a luetic meningomyelitis and the other was suggestive of tuberculosis. The calcification occurred variously about the hips and knees, never above the pelvis or below the knees. The lesions involved one joint only in thirty-three cases and were multiple in forty-six. In fifty-nine cases, one or both knees were the

* Read at the Annual Meeting of The American Orthopaedic Association, White Sulphur Springs, West Virginia, June 21, 1951.

site of the calcification. With the exception of three patients in whom there was persistence or return of sensation and voluntary motion, all had complete or almost complete cord or cauda equina lesions, without return of sensation or voluntary movement. Even in the three patients with less severe involvement, ability to walk did not return. It was Ceillier's opinion that the calcification was dependent upon several factors—the disturbance of the sympathetic and vasomotor mechanism, the initial oedema accompanying the lesions, and the immobility, the flaccidity of the tissues, and absence of muscle contractions. Secondary factors in the calcification, Ceillier believed, were due to lesions of the kidneys, heart, and liver, and to the phlebitides. In Ceillier's opinion, infection *per se* played no role.

As there were no associated joint changes in this series, rheumatoid disease and progressive ankylosing arthritis of the spine could be ruled out. Likewise, as in these para-osteo-arthropathies of Ceillier the processes were self-limiting, ossificans generalisata progressiva could be excluded. There was a similarity, though not an actual likeness, between these disorders and the tabetic and syringomyelic arthropathies, and joint disruption might occur if these patients were able to walk and subject their joints to trauma. In résumé Ceillier said that the medullary lesion seemed to play a considerable role in the genesis of para-osteo-arthropathies since it caused, more or less directly, a trophic alteration of the tissues, and since, indirectly, by causing the oedema and congestion it created an ossifiable "*milieu*." In accordance with the theory of unity of the connective tissues emanating from the blastoderm, the minute vascular ruptures and the extravasation of blood favored heteroplastic ossification of these tissues.

Finally in Ceillier's cases, the process of para-articular calcification began in the first few weeks or months following the primary injury and reached a maximum degree several months thereafter. The initial calcification proceeded to true ossification with bone trabeculation independent of the skeleton—usually in the connective tissues separating muscles.

Hans Voss, in 1937, wrote a long article on para-osteal and para-articular new-bone formation in systemic nerve disease. Voss included an extensive review of the literature, listing numerous reports on similar cases associated with other conditions, such as the calcification in tabes dorsalis and syringomyelia. Voss added four cases of his own, one accompanying a compression trauma of the cauda equina and three accompanying cerebral hemiplegia. Again the calcification occurred in the region of the hip joint and, in one case, in the region of the knee. In these cases the calcification also appeared either three to four weeks or several months after the primary trauma and progressed to true ossification. Of interest in Voss's article, as well as in Ceillier's, is the discussion of the etiological factors in the calcification,—namely, disturbed circulation associated with oedema and immobility, trophic factors, and trauma from passive exercise of the capsule, periosteum, and muscle fibers in the paralyzed limb. Voss believed that the neurotrophic factor was the most probable explanation of the etiology of the calcification, because the process stopped with the cessation of the degenerative phase of the pathological innervation and with the cessation of trauma to the trophic tissue.

Voss assembled from the literature a long list of lesions accompanied by para-articular calcification; these included epidemic encephalitis, cerebrospinal lues, arteriosclerotic hemorrhage and brain softening, traumatic brain injury, meningocele, extramedullary tumor, tabes dorsalis, syringomyelia, and others. Obviously, numerous irrelevant cases were included. The author has read many of the articles quoted by Voss and is of the opinion that relatively few of the cases should be included in this rather clear-cut picture of para-articular calcification following lesions of the central nervous system.

The earliest case report was that by Küttner in 1908, who, in discussing calcification following systemic disease, described a case of myelitis and myositis ossificans following measles; para-articular ossification occurred about the hip joints. The original paralysis had been incomplete.

In all of the cases reported by Ceillier and Voss the studies are based only upon roentgenograms and occasionally on tissue biopsy. The biopsies of Ceillier showed calcification in connective tissues and true ossification.

CASE REPORTS

The first two of three cases of para-articular calcification following anterior poliomyelitis here presented are reported through the courtesy of Dr. Michael Bonfiglio of Iowa City.

CASE 1. This patient was a twelve-year-old girl who was well until February 19, 1950, five days before she was seen at the State University of Iowa Hospitals, when headache, fatigue, marked malaise, and fever developed. Three days later she began having pain in both lower extremities which interfered with walking. The following day weakness developed in her lower extremities. The fever persisted during this period.

The physical examination revealed moderate rigidity of her neck and back. There was weakness of the neck flexors and extensors. The muscles of the left shoulder girdle and left forearm were weak. The right hip flexors and adductors, right knee flexors, and left foot dorsiflexors also showed moderate weakness. Findings in blood and urine examinations were normal. The lumbar puncture showed clear spinal fluid with 115 cells per 100 cubic centimeters; 37 per cent. were polymorphonuclear leukocytes; the rest were lymphocytes. The globulin test was positive. Spinal-fluid pressure was normal. The patient continued to have fever and progressively increasing paralysis developed during the next few days. She became incontinent of urine for several days. Except for motion in her hands, the patient had essentially total paralysis of both upper and lower extremities. Stiffness of the neck and back persisted and she complained bitterly of pain in her legs and arms. A low-grade fever and pain in both lower extremities persisted, particularly until April 9, 1950, seven weeks after onset, when swelling in her right foot and leg developed and her temperature rose to 101 degrees. The temperature elevation subsided in a few days. Because of tightness in the adductors and flexors of both hips, flexors of the knee and ankle, and adductors of the shoulder, the patient received physical therapy which included daily stretching of these tight areas, and active exercises. During the first week of June, fourteen weeks after the onset of poliomyelitis, pain and swelling in the right upper thigh along the anteromedial aspect developed. There was increase in local heat and reddening of the skin in this area.

Roentgenograms of the right hip revealed extensive ossification in the adductor region; a lesser amount was seen in the left adductor region. Ossification was present in the left paravertebral muscles and in the shoulders there was para-articular ossification, more extensive on the right than on the left.

Calcium was 10.6 milligrams per 100 cubic centimeters; phosphorus, 3.7 milligrams; alkaline phosphatase, 29.4 Jenner-Kay units. Urinary calcium excretion was increased. A biopsy of the mass in the right thigh showed ossification occurring in fibrous tissue. There was a small amount of cartilage in this area. Centrally, a small area of hemorrhage could be seen.

A section from the region adjacent to the muscle fibers shows more mature bony trabeculae with a narrow space filled with loose connective tissue.

Physical therapy was discontinued and the patient remained at bed rest. The pain and swelling began to subside.

Two months later roentgenograms showed diminution in the ossification at all sites. Calcium, phosphorus, and phosphatase levels were normal.

At this time doses of 600 roentgen units each were given to the right hip and left shoulder areas and doses of 200 roentgen units each were given as a palliative measure for the relief of persistent pain in the other areas.

CASE 2. This patient was a white male, twenty-two years old. The date of onset of poliomyelitis was August 3, 1949. He had urinary and fecal incontinence, paralysis of both lower extremities and the trunk, and partial paralysis of the right upper extremity. The cerebrospinal fluid showed 253 cells per 100 cubic centimeters. The patient became irrational and cyanotic. He required a respirator for three weeks and an indwelling catheter. Twelve weeks after onset he had pain and swelling of the left leg and thigh with a positive Homan's sign. A diagnosis of thrombophlebitis of the left lower extremity was made. There was residual swelling, mostly about the inguinal region and buttocks, for several weeks. At this time, some fifteen weeks after the onset of his disease, limitation of motion of the left hip was noted. Because of urinary-tract infection and bladder calculi, the patient was treated by the urologist for several months. When he was finally transferred to the Orthopaedic Service, a mass in the left hip region was noted.

Roentgenograms made on August 11, 1950, one year after onset of the disease, showed mature ossification in the region of the anterior superior spine over the left hip joint. This measured three by five by three centimeters upon surgical removal. Microscopic section showed a typical picture of ossification in connective tissue with the usual vascular intertrabecular tissue.

There has been much improvement in motion since removal of the mass.

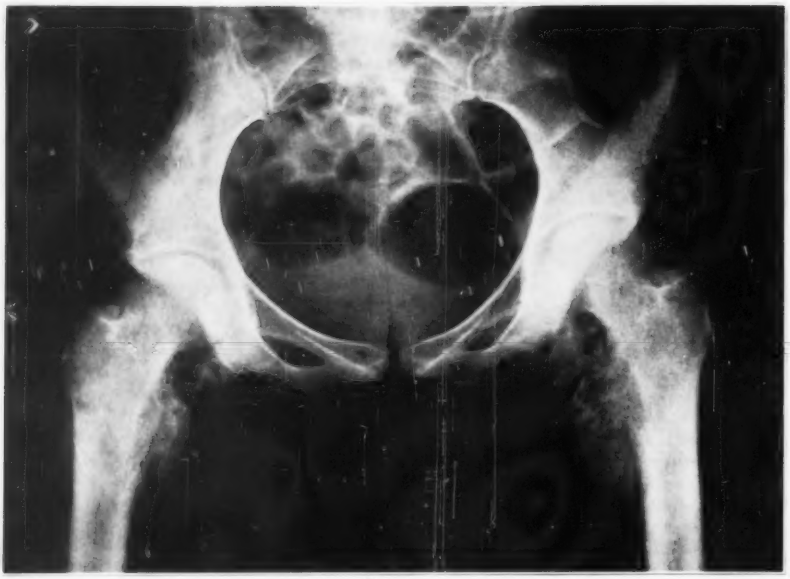

FIG. 1

F. P. Roentgenogram of pelvis including hip joints made January 13, 1944, about four months after onset of acute poliomyelitis, showing beginning para-articular ossification. Location of massive deposit anterior to hip-joint capsule and overlying base of femoral neck is not well visualized.

FIG. 2

F. P. Roentgenogram of pelvis made April 18, 1944, seven months after onset of poliomyelitis. Mature para-articular ossification can be seen.

In these two cases of Dr. Bonfiglio's there was no involvement of the hands and, in fact, in the second case, there was ossification only in a single area about the left hip joint.

CASE 3. September 20, 1943, F. P., a white, unmarried woman, thirty years of age, was admitted to the Contagious Unit of the Cincinnati General Hospital. The patient had worked in a war plant and had been an amateur athlete until September 14, 1943, when a cold developed; two days later there was low-back pain, and the following day weakness of both lower extremities. By September 20, 1943, both lower extremities were paralyzed. Paralysis rapidly extended to the arms, neck, trunk, and the respiratory muscles with the exception of the diaphragm. She could swallow liquids with difficulty. The patient was put in a respirator, where she remained continuously for seven weeks. For the ensuing several weeks she was delirious and disoriented. Temperature varied from 100 to 102 degrees Fahrenheit, occasionally rising to 103 degrees until December 1, 1943. During this period of her illness she had several attacks of pyelonephritis without calculi, which were controlled by sulfamerazine. Restlessness was controlled by barbiturates, which may have contributed somewhat to her disorientation. As she could not remain outside of the respirator at all, in spite of excellent nursing care, a rather large sacral decubitus developed which eventually healed. She was fed by gavage and intravenous fluids, including blood and plasma. From December 1 to 17, 1943, improvement was such that she could be removed from the respirator.

From September 21 to December 17, 1943, hot moist packs were applied continuously to the entire body. Once or twice daily, passive joint motion was carried out within pain limits. About December 1, ten weeks after onset, increasing stiffness in the hips, shoulders, and metacarpophalangeal joints was noted by the physical therapist, and passive motion became progressively more painful.

From December 1, 1943, to January 6, 1944, when the patient was transferred from the Cincinnati General Hospital to the Cincinnati Jewish Hospital, she had recovered completely mentally, was able to turn her head from side to side, and had slight active motion of her fingers. She had some intercostal muscle power and could swallow normally. The trunk and extremities still were otherwise completely paralyzed. By May 25, 1944, the patient could shrug her shoulders, flex the elbows against gravity, and contract the left rectus abdominalis and the lateral abdominal muscles. The left toe flexors, the left gastrocnemius, and the peroneals were active though rated as poor. The patient at this time was mentally alert and cooperative. Muscle power seemed to improve generally, though slowly.

On January 6, 1944, at the time of transfer from the Cincinnati General Hospital, hard fusiform masses of adventitious tissue were palpable in both axillae and groins. The left shoulder joint had just perceptible passive motion, as did the metacarpophalangeal joints of both hands, which were in complete extension. Passive motion in the thumbs was not limited. The hip joints could be moved, passively, some 20 degrees only.

On January 13, 1944, with great difficulty because of persisting pain on joint motion, roentgenograms (Figs. 1, 4, and 8) were made of all the extremities and spinal articulations. A moderate degree of metaphyseal osteoporosis was noted generally. As can be seen in the roentgenograms, in both axillary areas, both coxofemoral areas, and about the second to the fifth metacarpophalangeal joints of both hands there were diffuse calcified deposits with some areas of early ossification. These areas of calcification did not correspond to any specific muscle involvement or, apparently, to any particular fascial planes. From roentgenograms made subsequently (Figs. 2, 5, 6, and 7) it can be noted that the involved areas showed progressive ossification, so that on April 18, 1944, the process had become complete with true bone formation, including trabeculation. The left shoulder was ankylosed, but the other involved joints had slight passive mobility.

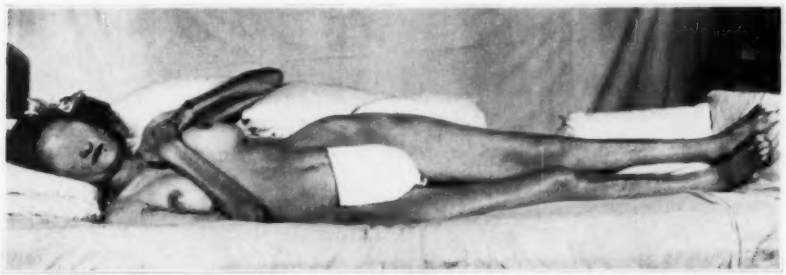

FIG. 3

F. P. Photograph of patient taken February 1944, five months following onset of poliomyelitis. The healed scars over the hip joints are sites of biopsies. Note the generalized wasting of extremities. The left shoulder is in fixed abduction at functional angle; the metacarpophalangeal joints are ankylosed in extension.

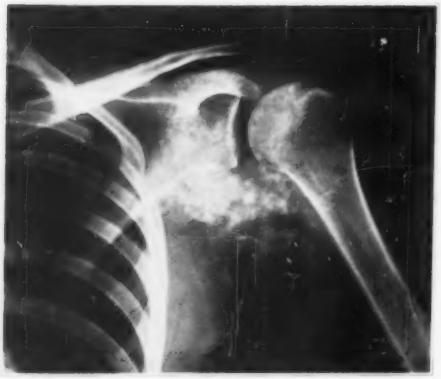

FIG. 4

FIG. 6

FIG. 5

FIG. 7

Figs. 4, 5, and 6: F. P. Roentgenograms of left shoulder joint, made four, five, and seven months, respectively, after onset of poliomyelitis. Transition from calcification to ossification, with massive shoulder-joint ankylosis, can be seen.

Fig. 7: F. P. Roentgenogram of right shoulder made seven months following onset of poliomyelitis. Mature para-articular ossification is seen, with slight shoulder-joint subluxation but no ankylosis.

In February, 1944, under local infiltration anaesthesia, biopsies were performed. From the left hip, skin only was removed as this area was believed to be infiltrated. Subcutaneous tissue, a section of the calcified mass, and a third section of muscle tissue from the tensor fasciae femoris were removed from the right hip. Little was learned from these biopsy sections, as they showed only fibroblastic infiltration, heterogenous calcium deposits in connective tissue, and incomplete degenerative changes in the tensor fasciae femoris.

TABLE I

Date	Serum Calcium (*Milligrams per 100 cubic centimeters*)	Serum Phosphorus (*Milligrams per 100 cubic centimeters*)	Phosphatase (*Bouansky Units*)	Alkaline (*King-Armstrong Units*)
January 7, 1944	10.8	5.0	14.7	31.9
April 8, 1944	10.8	4.8	8.5	19.7
May 12, 1944	10.8	4.9	4.9	—

On February 4, 1944, blood cholesterol, 278 milligrams;
On February 5, 1944, urinary creatinine, 0.522 grams in 24 hours;
urinary creatine, 0.696 grams in 24 hours.

Laboratory Data

Lumbar puncture was done September 21, 1943; spinal-fluid pressure was 130; 60 cells, all lymphocytes, were present. Total protein was 50 milligrams per 100 cubic centimeters. Routine blood-cell studies done repeatedly were not remarkable (Table I).

From the laboratory data there was no evidence of a generalized disturbance in protein metabolism, as in addition on January 17, 1944, the blood total protein was 5.94 grams, the serum albumin 4.14 grams, and the serum globulin fraction 1.80 grams. Of particular interest, however, are the alkaline phosphatase determinations, which showed, from January 17, 1944, when the calcification phase was still active, to May 12, 1944, when ossification was complete, 14.7 Bodansky units, compared with a final normal figure of 4.9 Bodansky units.

Subsequently, the following operative procedures were performed:

On March 16, 1945, eighteen months after the onset of poliomyelitis, under local infiltration anaesthesia and through an anterior incision over the right hip, an osteoma-like mass of new bone was exposed; this was found lying directly on the anterior capsule of the hip joint and fused only to the femur at the intertrochanteric area. This large mass of bone was easily removed after it had been osteotomized at its narrow attachment to the femur. Free passive hip motion followed.

On April 28, 1945, a similar procedure was done on the left hip. A single bone fragment measuring 3.75 centimeters by 8.75 centimeters was removed; this was again attached only to the intertrochanteric area of the femur at the site of the distal capsular insertion. The bone fragment was only slightly adherent to the underlying capsule and in the tissue plane beneath the rectus femoris and tensor muscles which, with the sartorius muscle, were pale and atrophic. Free passive motion, as in the right hip, resulted.

On April 17, 1947, under general anaesthesia and through three dorsal incisions over the metacarpophalangeal joints of the left hand, thin osseous plaques of bone were exposed; these were found lying on the joint capsules, bridging the joints, and fused proximally and distally, respectively, to the metacarpals and phalanges. After these narrow areas of osseous fusion had been severed, the new bone was easily separated from the underlying capsular tissue. Passive motion of 90 degrees could now be obtained at the second, third, fourth, and fifth metacarpophalangeal joints, the thumbs not having been involved.

FIG. 8

Fig. 8: F. P. Roentgenograms of hands, made four months following onset of poliomyelitis. Note that ossification of para-articular calcification is more advanced than in the x-rays of the shoulders (Fig. 4) and hips (Fig. 1) made on the same day. The first and fifth metacarpophalangeal joints are not involved in the process.

FIG. 9-A

FIG. 9-B

FIG. 10-A

(*See page 347*)

FIG. 10-B

FIG. 11-A

FIG. 11-B

Figs. 9-A and 9-B: F. P. Roentgenograms of the left and right hands made seven months after the onset of illness. Note mature para-articular ossification of the second, third, and fourth metacarpophalangeal joints.

Figs. 10-A and 10-B: F. P. Anteroposterior roentgenograms of the right and left hands made in 1949, two years after the partial excision of the para-articular new bone. Note the apparently normal metacarpophalangeal joint spaces.

Figs. 11-A and 11-B: F. P. Lateral roentgenograms of the hands made in April 1951, with the metacarpophalangeal joints in maximum active flexion. Passive flexion of these joints to 80 degrees is permitted. These views demonstrate maintenance of joint mobility four years after surgery.

On September 26, 1947, a similar operative procedure was done on the right hand because of the satisfactory result obtained on the left hand. The findings were identical, except that no true ankylosis existed between the fifth metacarpal head and the proximal phalanx of the fifth finger. Free passive motion resulted.

On December 9, 1948, the left hip was operated upon again because passive flexion was insufficient to allow sitting. On this occasion an extensive acetabuloplasty was done to remove the hooklike projection of bone extending anteriorly and inferiorly from the pubo-acetabular junction. Satisfactory passive motion was obtained.

At the present time (Figs. 6, 7, 11-A, and 11-B) the left shoulder joint is fused in an excellent position of function and the right shoulder joint, although flail, has about 20 degrees of passive motion in all directions. The hands have fair function with 80 degrees of metacarpophalangeal motion, although active flexion is limited by muscle weakness and no opponens power. Functionally, the hands are good. The patient has no muscle control in the hip joints, but she can sit in a wheel chair. Because of her obesity and the consequent difficulty of lifting her from the bed, she spends her time in a high Fowler position in bed. An ingenious person, she has become an amateur short-wave radio operator, controlling her set by remote controls, and has been supporting herself by selling stationery.

In presenting this unique case of acute anterior poliomyelitis with para-articular calcification resulting in eventual ossification, one might indulge in a good deal of speculation. However, the known facts alone will be reviewed.

In a search for additional cases, only four other instances have been found and none with involvement of the hands. One case reported by Drehmann has little significant data. Two cases reported to the author by Bonfiglio are quite similar without involvement of the hands; there is a fourth case, reported by Clinton Compere, about which the author has no specific data.

From the clinical course and the initial spinal-fluid studies, the diagnosis of acute anterior poliomyelitis may be accepted. Though the patient received hot moist packs and

passive joint exercise, the author does not believe that this therapy contributed to the process of calcification as these therapeutic measures were carried out carefully by a well-trained physical therapist. Although early blood phosphatase studies were not made, the subsequent determinations at four, seven, and eight months after the onset of the disease would indicate that a systemic disturbance of calcium metabolism existed for a limited period of time. During this period no calcium metabolism studies were made, but the variation from a high to a normal phosphatase figure corresponded with the ossification process of the anomalous areas of calcium deposit or, in other words, increased osteoblastic cellular activity. Unquestionably, in view of clinical findings, the patient had shown evidence of generalized convalescence from her illness. Therefore, the calcification and ossification processes may be considered to have been completed.

In comparing the roentgenographic illustrations in Ceillier's and Voss's articles, although their lesions are confined to the hip-joint and knee-joint areas, a close similarity between this case and theirs was noted. It may be concluded that, inasmuch as the reported cases represented para-articular calcification in a variety of severe lesions of the central nervous system, such a process may occur whenever there is an interruption of the central system due to the inflammation of either trauma or disease.

It is, furthermore, the opinion of the author that, though infrequent, this para-articular calcification with subsequent ossification is not so rare as it appears to be. In the majority of severe neurogenic lesions, whether they be acute anterior poliomyelitis or spinal-cord traumata, roentgenographic studies have been too infrequently made, as the indications for such studies have not been obvious.

In a similar case today, if therapy were feasible, peripheral vascular dilatation and vascular congestion of local tissue would be sought by various means, such as stellate and lumbar sympathetic ganglion blocks, trial use of priscoline (2-benzyl-, 5—imidazoline hydrochloride), and local superficial roentgen therapy or diathermy. However in this case, because of the severity of the acute illness, together with the required confinement in a respirator, local therapy was necessarily limited.

CONCLUSIONS

1. A case of acute anterior poliomyelitis is reported in which para-articular calcification and ossification developed, involving the metacarpophalangeal, shoulder, and hip joints.

2. This para-articular process, of an extent previously unreported, is due to an extensive lesion of the central nervous system and is non-specific to the type of this lesion, whether it be traumatic or inflammatory.

3. It is suggested that early local peripheral vascular stimulation might be beneficial in similar cases.

4. At the conclusion of the self-limited para-articular ossification surgical removal of the osseous masses re-established joint mobility.

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CONGENITAL KYPHOSCOLIOTIC TIBIA*

BY CARL E. BADGLEY, M.D., SYLVESTER J. O'CONNOR, M.D., ANN ARBOR, MICHIGAN, AND DONALD F. KUDNER, JACKSON, MICHIGAN

The term kyphoscoliotic tibia is suggested as a descriptive title for the deformity called by various authors "congenital bent tibia", "congenital kyphotic tibia", "intrauterine fracture of the tibia", and "congenital bowing of the tibia". There is need for a precise title properly to differentiate this clinical entity.

Although occasionally the bowing of the tibia occurs chiefly or entirely in one plane, the majority of these patients present an anterior or posterior bowing associated with a lateral or medial rotational deformity akin to that seen in kyphoscoliotic spines. The term "kyphos" means a hump or deformity in an anteroposterior direction and scoliosis signifies lateral deviation; the descriptive term seems applicable to this deformity.

Congenital kyphoscoliotic tibia may be divided into the following clinical groups:

1. Tibia with anterior bowing.
2. Tibia with anterolateral or anteromedial bowing.
3. Tibia with posterolateral or posteromedial bowing.
4. Anterior kyphoscoliotic tibia with cystic areas (prepseudarthrotic type).
5. Anterior kyphoscoliotic tibia with pseudarthrosis.

Congenital bowing of the tibia may be produced by lesions from general causes, such as osteogenesis imperfecta, achondroplasia, and chondrodystrophy. However, the characteristic features of the localized deformity in congenital kyphoscoliotic tibia readily differentiate this lesion, both clinically and roentgenographically, from bowing produced by these general causes.

CHARACTERISTIC FEATURES

The characteristic features of this clinical entity can best be illustrated by selected cases. A careful review of the cases reported in the literature shows complete accord with the clinical features noted in the twenty new cases recorded in this study. There can be very little question as regards the identity of the lesion presented in each case.

The characteristic features may be outlined as follows:

1. Congenital bowing of the tibia is a constant feature, with anterior or posterior convexity, generally associated with rotation and a lateral or medial bowing.

2. The lesion occurs uniformly in the distal portion of the central third of the tibia.

3. Roentgenographically an ossified mass is constantly found at the site of deformity on the concave side of the curve. The trabeculations in this dense area are generally arranged radially from the apex of the curve, and usually do not lie in the axial direction.

4. Pathologically, there is evidence that the lesion is located primarily in the diaphyseal center, at a site corresponding to the location of the original primitive mesenchymal bar, and the site of origin of the early cartilaginous anlage for the primary ossification center. The lesion may persist for years in the lower portion of the central third of the tibia. Repeated roentgenograms, over years of study in individual cases, demonstrate that normal bone growth occurs from the epiphyseal ends. Delay in ossification of the lower tibial epiphysis is commonly noted, but normal ultimate development is the rule.

5. The capability of spontaneous correction of the deformity, especially in those cases with posterior bowing, will be particularly stressed in this paper. Recently Heyman informed us of a similar finding in his cases. Correction of anterior bowing does occur, but

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TABLE I

SUMMARY OF KNOWN DATA ON TWENTY CASES OF CONGENITAL KYPHOSCOLIOTIC TIBIA

Case No. Hosp. No. Initials Sex	Age at Beginning of Observation Period	Bowing Deformity	Visible Marrow Cavity at Apex of Bone	Associated Deformities	Dimpling of Skin at Apex	*Café au lait* Skin Marks	Definite Evidence of Neurofibromatosis	Spontaneous Correction of Deformity		Fibula Shows Similar Deformity
								Yes or No	Period of Observation	
1 No. 613894 Male	3 yrs.	Anterolateral	None apparent	None	None noted	Yes	Yes, of eyelid	Improving		Yes
2 No. 547140 Female	6 yrs.	Posteromedial	Yes, patent	Talipes calcaneus, shortening of 1 inch	None noted	Yes	None	Yes	6 years (by mother)	Yes
3 No. 02303 L. C. Female	12 yrs.	Posteromedial	Yes, almost normal	Talipes calcaneus, shortening of 2 inches	None noted	Yes	None	Yes	12 years (by mother)	Yes
4 No. 32975 T. R. Male	14 yrs.	Anterolateral	Yes, markedly abnormal	Talipes calcaneo-valgus Spinal kyphoscoliosis $\frac{1}{2}$ inch shortening	None noted	Yes	None noted	Yes	14 years (by mother)	No deformity apparent
5 Female	7 mos.	Anterior	Yes, constricted	1$\frac{1}{2}$ to 2 inches shortening Absence of fibula	Yes	Yes	None noted	Yes	3$\frac{1}{2}$ years	
6 No. 576324 E. C. Male	2 yrs.	Anterolateral	Yes, constricted	Absence of foot and of distal tibial and fibular epiphyses	None noted	None noted	None noted	None noted	6 years	Yes
7 L. B. Male	2 yrs.	Anterior	Yes, constricted	2$\frac{1}{2}$ inches shortening Talipes valgus Absence of talus and fibula	Yes	None noted	None noted	None noted		

(Table I—*Continued*)

8 No. 560587 J. E. M. Female	15 mos.	Anterolateral curve Cystic change in posterolateral position of tibia at level of apex Cystic changes in fibula at apex	Yes, constricted	Suggestive shortening of fibula at proximal end	None noted	Yes	None noted	None noted	No follow-up	Yes
9 No. 658595 D. H. Male	6 mos.	Anterolateral	Yes, virtually normal	Absence of fibula and fifth ray Maldevelopment of femur	None noted	None noted	None noted	None noted	3 yrs.	None
10 No. 623286 J. M. M. Female	3 yrs.	Anterior	Yes	Absence of fourth and fifth rays Syndactylism of right hand Fusion of terminal phalanges 3rd and 4th fingers Deformity of right femur Absence of fifth ray of right foot	None noted	Yes	None noted	Yes, marked	2 yrs.	
11 Male	2 wks.	Posteromedial	None apparent	Talipes calcaneus, 1½ to 2 inches of shortening	None noted	None noted	None noted	Yes	5 yrs.	Yes
12 No. 609064 J. G. M. Male	1 wk.	Posteromedial	Yes, marked constriction	Talipes calcaneo-valgus	None noted	None noted	None noted	Yes	1 yr. and 7 mos.	Yes
13 Male	Infant	Posteromedial	None apparent	None noted	None noted	None noted	None noted	Yes	5 yrs. and 7 mos.	Yes
14 No. 637990 G. S. Female	Infant	Anterolateral	Yes	Talipes equinovarus Absence of fifth ray and 1 inch shortening	Yes	None noted	None noted	Yes	2 yrs.	Yes

(Table I—*Continued*)

Case No. Hosp. No. Initials Sex	Age at Beginning of Observation Period	Bowing Deformity	Visible Marrow Cavity at Apex of Bone	Associated Deformities	Dimpling of Skin at Apex	*Café au lait* Skin Marks	Definite Evidence of Neurofibromatosis	Spontaneous Correction of Deformity		Fibula Shows Similar Deformity
								Yes or No	Period of Observation	
15 No. 643162 P. McL. Female	2 mos.	Anterolateral	None apparent	Definite constriction of tibia	Yes	Yes	None noted	None	5 yrs.	Yes
16 W. DeW. Male	1 yr. and 2 mos.	Anterior	Yes—a faint line is apparent	Cystic area anteriorly Spontaneous fracture followed by pseudarthrosis	Yes	Yes	None noted	None	2 yrs.	Yes
17 L. I. Male	4 mos.	Anterolateral, reported	None apparent	Marked constriction of both bones Pseudarthrosis after fracture from a fall Talipes equinovarus Contracted triceps surae 3 inches of shortening	Yes	Yes	None noted	No	5 yrs.	Yes
18 No. 650542 D. W. Female	34 yrs.			Spontaneous fracture at age 4 followed by pseudarthrosis Pseudarthrosis of radius and ulna at 3 years of age	None noted	Yes	Yes	No	33 yrs.	Yes
19 R. M. B. Male	2 wks.	Anterolateral	None apparent	None noted	None noted	None noted	None noted	Yes	2 yrs. and 10 mos.	No
20 No. 502338 J. McC. Male	10 mos.	Anterolateral	Yes, patent but slightly narrowed	Talipes calcaneus	None noted	Yes	None noted	No, operative correction	3 mos.	Yes

a residual deformity may persist. Ten of the twenty cases in this series showed a definite tendency to spontaneous correction.

6. There is a very marked potential danger of pathological fracture in these cases, and non-union is a common complication. Not infrequently non-union has developed after a fracture which occurred during manipulation or during an operative attempt to correct the deformity. Pseudarthrosis is particularly apt to occur in cases of anterior bowing associated with roentgenographic evidence of cystlike changes in the tibia. In three of our twenty cases, spontaneous fracture and pseudarthrosis developed.

7. In the cases recorded elsewhere, as well as in the twenty cases in the series here presented, associated deformities occurred with such frequency that they must be regarded as a definite part of the clinical entity, even though they are not a constant finding. The associated deformities in our group may be classified as follows:

A. Hypoplasia: This includes failure of development involving part or all of (1) the fibula, (2) the fourth and fifth rays of the foot or the fifth ray alone, (3) the talus, (4) the proximal end of the femur; and congenital amputation of the foot and ankle.

B. Hyperplasia or partial gigantism may occur. This occurred in two of our cases, in one as an enlargement of the index finger and thumb, in the other as an enlargement of the big toe.

C. Syndactylism is occasionally present.

D. Skin lesions occur with a relatively high frequency. *Café au lait* markings were found in ten cases. Neurofibromatosis was present in three of our cases.

E. There may be deformity of the feet, such as talipes calcaneus, calcaneovalgus, and equinovarus. These conditions are also encountered frequently. Fifteen of our twenty patients presented such associated deformities of the feet.

8. Frequently an associated dimpling of the skin at or near the apex of the curved tibia is present. Eleven of our twenty patients presented this.

ILLUSTRATIVE CASES

Of the twenty patients who comprise the authors' series (Table I), the following ten are presented in detail to illustrate various features characteristic of congenital kyphoscoliotic tibia.

Dense Bony Mass on Concave Side of Bone

An outstanding roentgenographic characteristic of this group is the dense bony mass on the concave side of the curve. The thickening is greatest at the apex of the curve extending almost to the anterior cortex of the tibia; a marrow cavity is not visible. From this area the bony mass slopes gradually toward the epiphyseal ends of the diaphysis on the concave side of the curve. The dense bone has an entirely different structural pattern from that in the metaphyseal ends of the tibia, which has normal cortical trabeculation and density. The trabeculations of the dense bone on the concave side radiate from the apex of the curve rather than lie in the axial alignment as in the normal tibia.

In Case 1 (Fig. 1) the tibia was bent in an anterior and lateral plane, with the apex of the curve in the distal portion of the middle third of the tibia. The fibula in this case seemed to follow the curve of the tibia.

Spontaneous Correction of the Deformity

Spontaneous correction of the deformity in this condition can occur (Figs. 3-A and 3-B and Cases 2, 3, 11, 12, 13). Indeed the natural tendency in cases without complications in which treatment was never undertaken is one of gradual correction by normal bone formation from the epiphyseal ends, with a very slow remodeling of the involved central segment of the tibia. There may be retention of the bowed segment, but the mature tibia presents a minimal deformity, although a certain amount of shortening persists.

FIG. 1

Fig. 1: Case 1. August 4, 1948. Roentgenogram illustrating the characteristic findings in anterolateral bowing of the tibia.

Fig. 2: Case 4. May 3, 1949. This fourteen-year-old boy had a history of congenital bowing of the tibia. The dense cortical mass on the posteromedial portion of the shaft persists, but the axial alignment is becoming normal by distal and proximal growth. The normal tibia is shown to the right.

FIG. 2

CASE 2 (Fig. 2). Male, fourteen years old. According to the mother there was a history of anterolateral bowing of the tibia associated with a calcaneovalgus deformity of the foot. The patient also presented a congenital kyphoscoliosis of the spine. On e-half inch (1.25 centimeters) of shortening persisted. Comparison of roentgenograms of the normal with those of the involved tibia demonstrated the lateral curvature on the affected side. There was retention of the dense mass on the concave side of the tibia in the central portion, with normal growth from the epiphyses tending to produce correct axial alignment. The marrow canal was not normally developed on the central portion. The abnormal characteristics of the dense bony mass on the concave side persisted.

CASE 13 (Figs. 3-A and 3-B). Male infant. Clinically this patient demonstrated a posteromedial bowing of the tibia. Anteroposterior and lateral roentgenograms, made in 1938, showed the characteristic changes.

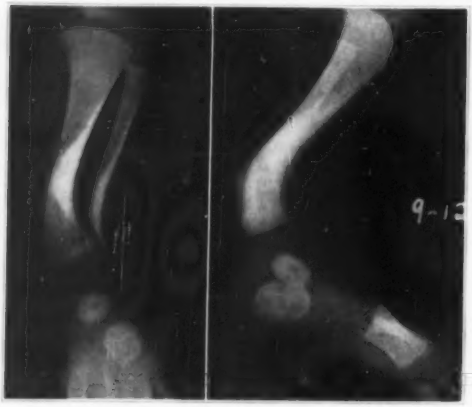

FIG. 3-A

FIG. 3-B

Fig. 3-A: Case 13. September 12, 1938. Anteroposterior and lateral roentgenograms demonstrating posteromedial bowing of the tibia.

Fig. 3-B: April 19, 1944. Six years later there is almost complete correction of the condition.

FIG. 4

FIG. 5

Fig. 4: Case 8. October 12, 1944. Anteroposterior and lateral roentgenograms showing anterolateral bowing of the tibia.

Fig. 5: Case 9. January 27, 1947. The roentgenogram demonstrates the hypoplastic changes frequently associated with bowing of the tibia. Note absence of foot and ankle and short proximal portion of the tibia and fibula.

(It is to be noted that the younger the child, the more marked is the characteristic dense bony mass.) The medullary canal appears closed. Six years later, April 19, 1944, the roentgenograms showed excellent correction of the deformity; the central position of the deformed segment was again evident. There was normal epiphyseal growth of the tibia.

Posterior Bowing

Characteristically the cases of posterior bowing undergo spontaneous correction and do not appear to fall into the so-called prepseudarthrosis group, to be described. We have no example of pseudarthrosis arising in a tibia with posterior angulation.

Cystic Changes

Cystic changes are also encountered frequently.

CASE 8 (Fig. 4). Female, fifteen months old. Roentgenographic findings at the time when the authors first saw this patient included anterolateral bowing, with a dense bony mass on the concave side of the tibia. There was evidence of cystic change in the posterolateral surface of the tibia at the level of the kyphosis, associated with cystic change in the fibula and apparent fracture. Suggestive shortening of the proximal end of the fibula was also noted. Conservative treatment was advised; unfortunately this patient was lost to follow-up.

Associated Deformities and Other Conditions

Hypoplasia, hyperplasia, and syndactylism, as well as various deformities of the feet, *café au lait* skin marks, and neurofibromatosis, are not uncommon (Table I and Case 9, Fig. 5).

Prepseudarthrosis

We agree with J. R. Moore[27] that the classification of prepseudarthrosis is plausible and advisable in this condition. The following cases fall into the category of prepseudarthrosis.

CASE 15 (Figs. 6-A to 6-C). P. McL., aged two months when first seen. Roentgenograms made May 18, 1943. The anteroposterior roentgenogram showed typical anterior bowing associated with lateral bowing. The lateral view illustrates an important feature which we have not seen described previously. There was a definite narrowing of the tibia in the deformed area with an apparent closure of the marrow canal. This would

seem to indicate that the primary perichondrial collar had become constricted and had failed to add bone circumferentially. The marrow canal was closed.

(The authors wish to emphasize the importance of this constriction at the site of the curvature.)

At re-examination August 11, 1944, the deformity was more marked. There was the typical ossified dense mass on the concave side of the curve together with an attempt, apparently, at marrow-canal formation in the proximal portion of the deformed mass. Four years later, August 4, 1948, the lateral bowing was centrally placed and perhaps more marked. The anterior bowing remained constant. A suggestive cystic area was seen in the proximal portion of the abnormal area. The marrow canal was not yet restored, but there was normal growth from the epiphyseal ends.

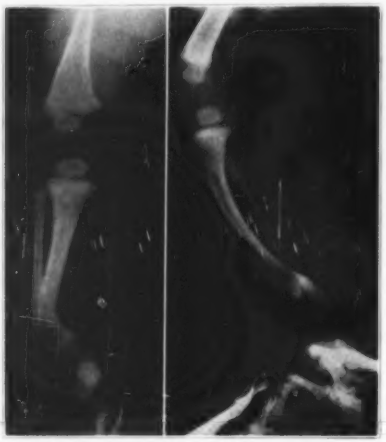

FIG. 6-A

Case 15. May 18, 1943. There was marked narrowing or closure of the marrow canal.

This is the type of case in which pseudarthrosis might develop from a spontaneous fracture. Kite has reported on three patients, seen prior to fracture, in whom spontaneous fracture occurred. We have two such cases in our group of young patients, and have included a third, an adult with a history of fracture occurring in a congenital curved tibia.

Pseudarthrosis

Pseudarthrosis may develop after birth in patients with bowing of the tibia.

CASE 16 (Figs. 7-A and 7-B). W. DeW., male, aged fourteen months. The roentgenogram made October 31, 1944, showed more clearly than in any

FIG. 6-B
August 11, 1944

FIG. 6-C
August 4, 1948

Figs. 6-B and 6-C: The deformity was progressive and the canal was not restored. This type of deformity may easily progress to a pseudarthrosis. The constricted area is suggestive of the initial "bone collar" in beginning ossification of the tibia.

FIG. 7-A

FIG. 7-B

FIG. 8

Fig. 7-A: Case 16. October 31, 1944. This case presents the characteristic structure of the dense mass of ossification on the concave side of the curve.

Fig. 7-B: October 14, 1946. A spontaneous fracture with a true pseudarthrosis has occurred at the junction of the cystic area to the dense bone mass, the usual site for a spontaneous fracture.

Fig. 8: Case 17. April 11, 1947. Anteroposterior and lateral roentgenograms showing the development of a pseudarthrosis of the tibia following fracture of the bowed tibia.

of our other cases the true character of the dense ossified mass on the concave side of the curve. There was an arc of bone separated by a faint line from the true tibial outline, with trabeculation running radially instead of axially toward the apex of the kyphos. This constant dense bone mass had the appearance of an infarct in the anlage of the primary cartilaginous bar for the tibia. It does not seem likely that the constancy of appearance and the characteristic retention of the whole posterior arc of the tibia could result from

FIG. 9-A

FIG. 9-B

Fig. 9-A: Case 19. April 16, 1946. Roentgenograms showing anterolateral bowing of tibia, with an unusual ossification mass.

Fig. 9-B: February 4, 1949. As bone growth from the epiphyses progressed, the area of involvement became relatively smaller.

new-bone formation outside the original anlage without an alteration in the outline of the tibia. In this case the bent tibia showed evidence of dysplasia of central origin rather than new-bone deposition on the cortex. The cystic area extending anteriorly over this dense bone appears to be an attempt to form a central marrow cavity which is not present in the ossified mass. At re-examination on June 28, 1945, the anteroposterior view showed the marked anterior bowing. No changes were evident in the lateral view. Spontaneous fracture occurred after this date, with development of a typical pseudarthrosis in the distal portion of the ossified mass and apparently through the line separating this mass from the tibia (Fig. 7-B).

FIG. 10-A

Case 20. April 15, 1942. Anteroposterior and lateral roentgenograms showing anterolateral bowing of tibia.

Amputation was eventually performed. No neurofibroma was found in the specimen. The pathological findings showed only advanced reparative proliferation with much newly formed connective tissue, cartilage, and osteoid tissue.

The location of the fracture in pseudarthrosis of the tibia coincides with the upper or lower arc of the ossified mass. The fracture is akin to the collapse of bone which may occur in aseptic necrosis at the junction of the necrotic and the viable bone.

CASE 17 (Fig. 8). Male, aged four months. On May 15, 1942, the child fell in his play pen and fractured the right tibia.

FIG. 10-B

FIG. 10-C

Fig. 10-B: Roentgenograms made twenty-six months later, June 24, 1944, reveal persistence of the deformity.

Fig. 10-C: December 21, 1945. Roentgenograms made three months after osteotomy, which was done through almost normal bone rather than at the site of the primary ossification mass.

Pseudarthrosis developed. The original roentgenograms are not available, but the report describes a severe anterior and lateral bowing of the tibia with evidence of a healing fracture of the fibula. Roentgenograms made July 16, 1945, showed a typical pseudarthrosis of the tibia and fibula.

The pseudarthrosis in these cases is not congenital but follows fracture of a congenitally malformed bone. The bone ends have the typical conical shape of atrophic non-union.

It was thought best to delay operation until the child was older; braces were employed for support.

On April 11, 1947, roentgenograms showed the pseudarthrosis persisting (Fig. 8). Amputation was carried out, as there was shortening of three inches, an equinovarus deformity, and a contracted heel cord.

In these cases there is no doubt that pseudarthrosis developed from a congenital bowing of the tibia and fibula by spontaneous fracture. A high incidence of spontaneous fracture in congenital bowing of the tibia, and of fracture following surgical correction has been reported in studies of "congenital" pseudarthrosis [3,10,26,27,35].

Unusual Ossification Mass

Case 19. R. V., male, aged two weeks, presented a somewhat different aspect of the ossified mass. In the roentgenograms (Figs. 9-A and 9-B) the mass on the concave side was less dense than usual. The outlines of the cortex of the tibia seemed to be pointed as though pinched as they approached each other at the height of the covexity. The ossified mass on the concave side might be considered to be ossification under the periosteum, following the interpretation of Caffey and others. On the other hand, here again the location of this ossified mass and its triangular appearance may well mean an interference in growth of the primitive mesenchymal mass, while normal ossification proceeded above and below it. Three years' observation of this case is illustrated to show the normal growth from the ends of the tibia and the gradual correction of the deformity from this new growth. The essential deformity at the kyphotic area has remained, however, and at the last examination the posterior cortical surfaces still presented a pointed appearance, with increased density in the ossifying mass.

The history of this case is of interest in that a diagnosis of intra-uterine fracture was made at birth. When the patient had a fall at the age of nineteen months, a diagnosis of fracture was again made. However, spontaneous correction of the deformity has been taking place gradually.

Operative Correction

There was only one patient in this series on whom an operation was performed. We wish to emphasize particularly that surgery should be delayed until normal bone has developed through which correction can be made.

Case 20 (Figs. 10-A to 10-C). Female, born June 18, 1941, aged ten months. The patient presented anterolateral bowing, associated with a calcaneus deformity of the foot. A roentgenogram made April 15, 1942, showed the characteristic bowing of the tibia. Narrowing of the segment of the tibia is noted at the level of the curve in the lateral view.

Roentgenograms made June 24, 1944, revealed persistence of deformity.

In September 1945, operative correction of the deformity through healthy bone below the curve was performed; operation was undertaken reluctantly, upon the insistence of the mother.

Roentgengrams made December 21, 1945, showed that union had occurred with correction. According to a verbal report from Colonel Rylander in 1949, the patient had "an excellent result".

REVIEW OF EMBRYOLOGICAL, HISTOLOGICAL, AND CLINICAL STUDIES OF NORMAL AND ABNORMAL BONE GROWTH

It seems clear that an explanation for the pathogenesis of this condition must be based on a consideration of the characteristic features reported in these twenty cases. Middleton's concept of a primary contracted calf muscle producing the kyphotic tibia does not explain the associated deformities, nor does it account for the posterior bowing of the tibia. The often quoted, but never proved, "fracture *in utero*" obviously cannot be regarded seriously.

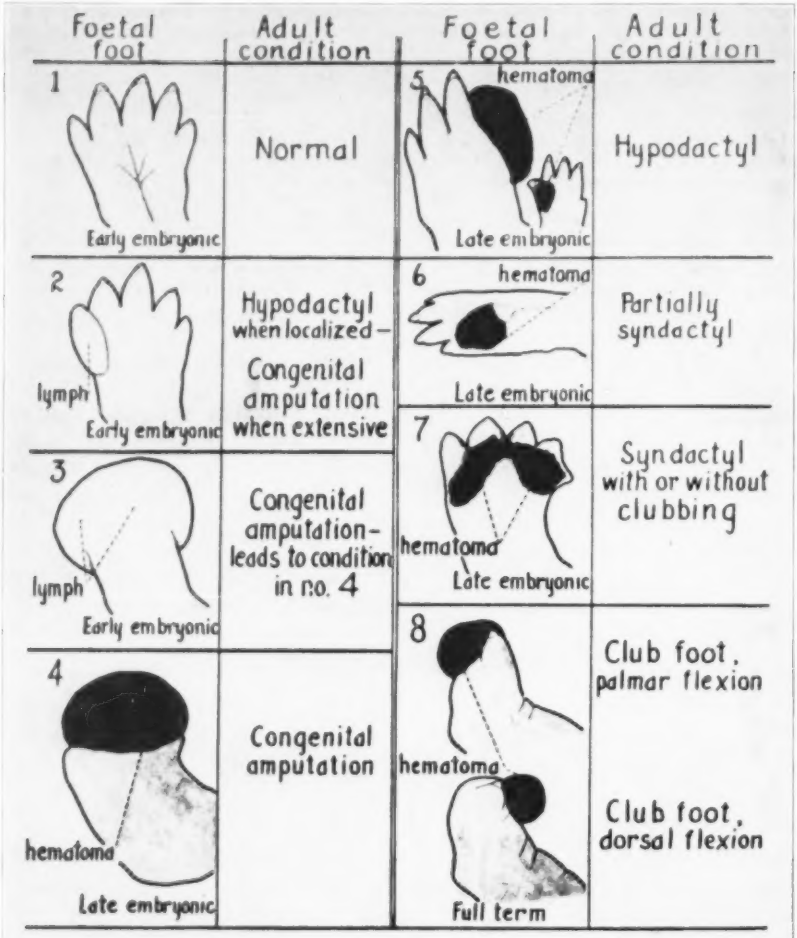

Chart B This chart illustrates the early and late foetal abnormalities of the limbs and the abnormal structural conditions of the limbs at birth, and indicates the probable condition of these members in later life. The adult condition is indicated to the right of the illustrated abnormality.

FIG. 11

Showing early and late foetal abnormalities in limbs. (From H. J. Bagg: Hereditary Abnormalities of the Limbs, Their Origin and Transmission, *American Journal of Anatomy:* **43,** 190, 1929. Reproduced by permission of The Wistar Institute of Anatomy and Biology, Philadelphia.)

Café au lait markings and other evidence of neurofibromatosis are changes which have been noted. Beveridge Moore in several excellent papers [24, 25] has called attention to the high frequency of neurofibromatosis and abnormality of nerve structures occurring in congenital lesions. He did not state, however, as have some subsequent authors, that the neurofibromatosis or the nerve changes were the cause of the lesion. He reported an incidence in congenital deformities of 91 per cent., or seventy cases out of seventy-eight, with definite pathological changes of the peripheral nerves. Twenty-four of these demon-

strated neurofibromatosis. He questioned the cause of the nerve changes and emphasized the frequency of this coincidental finding. A theory of neurogenic origin of this lesion has been advanced without, however, definite knowledge of the pathomechanics.

Corsi has defined "congenital curved tibia" as a segmental dysplasia of the skeleton of the leg at the junction of the upper two thirds with the lower third. Fifty per cent. of his patients presented posterior rather than anterior bowing. Corsi agrees with Codivilla that the condition is due to absence of blood supply and disorganized deposition of lime salts. He stated that the poor formation of bone trabeculae and the loss of normal elasticity and solidity of bone lead to such secondary factors as hazards from numerous muscular actions and from pressure by the amnion, and may possibly place the foetus in an abnormal position.

Codivilla has suggested vascular insufficiency in embryonic life as the cause for defective development. Bocchi, influenced by this theory, reported a case of congenital pseudarthrosis in which a specimen was examined by arteriograph after amputation. The blood vessels were hypoplastic and irregular. Patten has expressed the opinion [32] that, if there were a vascular disorder, this probably occurred at the time of existence of the foetal blood channels, before the development of the blood vessels.

Bean, studying congenital bone defects in the descendants of mice treated with roentgen rays, felt that the bone changes in this group (previously reported by Bagg) were on a neurovascular basis. She concluded that "the many types of abnormality, occurring simultaneously in the same stock of mice, seem to point to one underlying cause and its possible modifications" and that "the most workable theory . . . is one of developmental arrest resulting from different degrees of failure of blood and nerve supply". The kyphoscoliotic tibia with its associated deformities is similar to the simultaneous lesions noted in the descendant mice.

Warkany in his studies of congenital malformations [26, 28] induced by maternal nutritional deficiency came to the conclusion that histological studies show that malformations are already present in cartilaginous structures, indicating that the deviation from normal development occurs before or at the stage of chondrification [38]. He found that riboflavin, a vitamin known to be necessary for normal growth in rats, is also necessary for normal embryonic differentiation [38].

Bagg has demonstrated inherited anatomical defects of the limbs in the descendants of mice treated by roentgen ray. By operative exposure and visualization of the transparent uterus of the mice he actually observed the development of club-foot, hypodactylism, congenital amputation, syndactylism, and polydactylism. He was able to observe the early lesions in the extremities and to follow the development of the deformities. As the embryo grew, he had evidence of the early lesion and the resultant deformity. Of 5,280 animals of the abnormal strain, 432 had demonstrable foot defects. He observed that the earliest defect was associated with the formation of a bleb, which locally raised the epithelium of the anlage for the foot. Later there was an escape of blood into the bleb and the formation of a localized blood clot. The blood clot may persist until birth. An example of this was a foetal foot which suffered developmental arrest from unknown causes. There was a breakdown in the lymph circulation producing a bleb, followed by a breakdown of the blood supply and hemorrhage with resultant blood clot. The final result was destruction of the entire foot—a so-called congenital amputation. In another case, a smaller hemorrhagic lesion, more superficially placed, produced syndactylism in the mature animal. Another lesion in the foot, slightly deeper but localized to a developing digit, produced hypodactylism. If the hematomata were large, exerting pressure on the musculature or tendons, clubbing of the foot occurred (Fig. 11).

The results of Warkany's and Bagg's brilliant studies of artificially produced congenital deformities in mice and rats observed during prenatal and postnatal phases of development must prove of considerable significance in our understanding of the abnor-

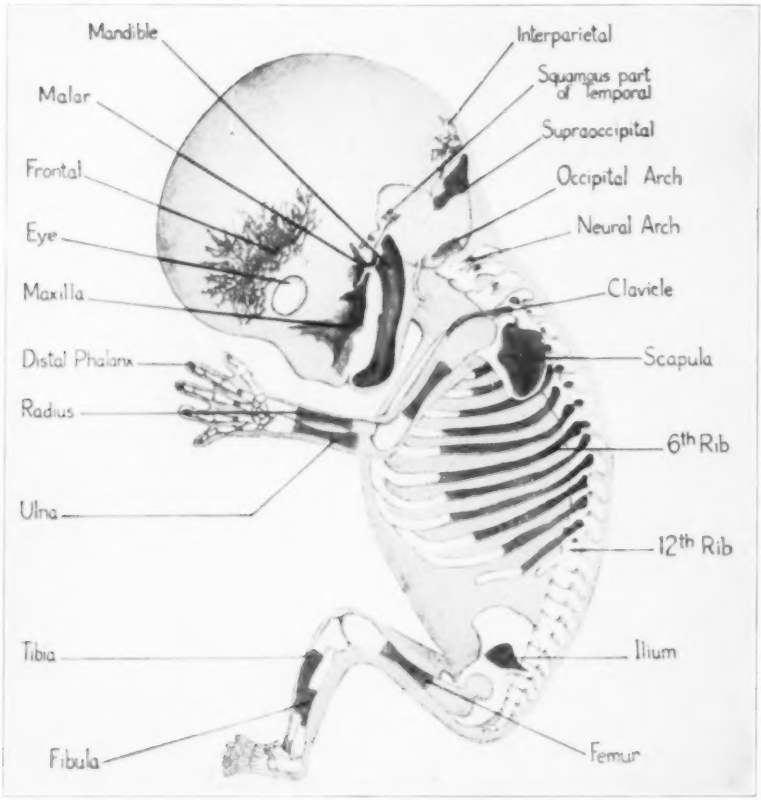

FIG. 12

This illustration of a human embryo shows the origin of the tibial ossification center to be in the central third. Anterior bending is a normal process in the embryological ossification of the tibia. (Reproduced by permission of The Blakiston Company, Philadelphia, Pennsylvania, from Human Embryology, p. 286, 1946, by B. M. Patten.)

malties of the development in the human embryo. It is of great importance to note that the lesions leading to these deformities occurred very early in foetal life, in the precartilaginous phase of embryonic skeletal development.

NORMAL EMBRYOLOGICAL DEVELOPMENT OF THE TIBIA

The normal development of the limb bud presents a logical sequence of events. The authors believe that it is possible to determine the point in this sequence at which the departure from normal to abnormal, specifically the development of congenital kyphoscoliotic tibia, takes place.

In an excellent study by Carey the development of the pig femur is thoroughly described from the period of the undifferentiated mesenchyme to the ossified femur at the time of birth. Briefly, Carey demonstrates that there is an early condensation of the mesenchyme in the center of the limb bud called the scleroblastema. From this, a membranous skeleton develops which differentiates into the cartilaginous skeleton. The osseous skeleton replaces the cartilaginous structure.

The embryonic cartilage forms slightly distal to the center of the femoral shaft. During the ensuing period of cartilaginous differentiation, rotation of the hind limb begins;

FIG. 13

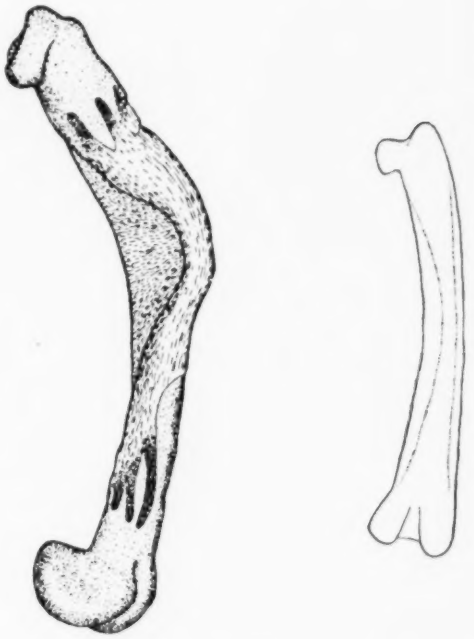

FIG. 14

Fig. 13: Longitudinal section of tibia, showing early development of ossification; the center is in the mid-shaft area. *A:* insertion of quadriceps tendon; *B:* dense primitive connective tissue. (Reproduced by permission of J. B. Lippincott Company, Philadelphia, Pennsylvania, from Tumors of Bone, Ed. 3, p. 73, 1949, by C. F. Geschickter and M. M. Copeland.)

Fig. 14: Abnormal development of the femur (developed as a chorio-allantoic graft) of a chick embryo six days old is shown in comparison with a normally developed femur in a fifteen-day-old chick embryo. (Reproduced by permission of The Cambridge University Press, London, England, from Bones: A Study of the Development and Structure of the Vertebrate Skeleton, p. 32, 1936, by P. D. F. Murray.)

simultaneously a marked bending may be detected in the femoral cartilage shaft. A dense fibroblastic perichondrium develops on the convex side, denser at the summit and more rarefied at the proximal and distal extremities. On the concave side the tissue is looser in texture and the capillaries approach the cartilage. In the scleroblastemal stage, there is a period of accelerated longitudinal growth. Carey quotes Bardeen, Holl, and Schomburg who found that during the period of accelerated development in human embryos—when the embryo is from fifteen to twenty millimeters long—the femur "may extend so rapidly in length as to become temporarily distorted by resistance at the ends". He believes that this distortion is an accentuation of the normal bending of the femur which occurs at the beginning of limb rotation. The cause of this deformity is the resistance to longitudinal femoral growth. Carey has demonstrated that muscle differentiation and activity are manifested in the thigh musculature of pig embryos seventeen millimeters long; that limb rotation begins in embryos nineteen to twenty-two millimeters long; that the cartilaginous anlage of the femur takes the form of a bent beam in embryos at the beginning of limb rotation; and that the first evidence of unequal osteoblastic proliferation is seen in the femora of embryos twenty-six to thirty millimeters long.

Ossification produces a definite, unequal constriction at the middle of the cartilage rod. The zone of osteoblastic invasion is more elongated and more extensive on the convex than on the concave side of the femoral rod. The primordial periosteum is denser at the site of maximum tensile strength on the convex than on the concave side of the femoral

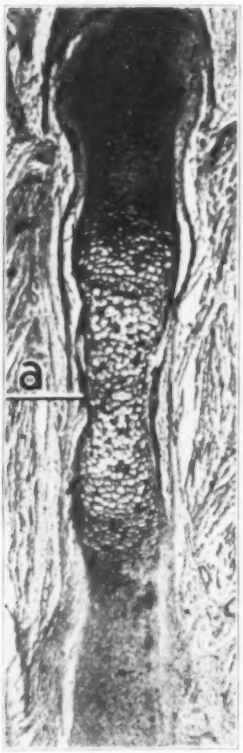

FIG. 15-A

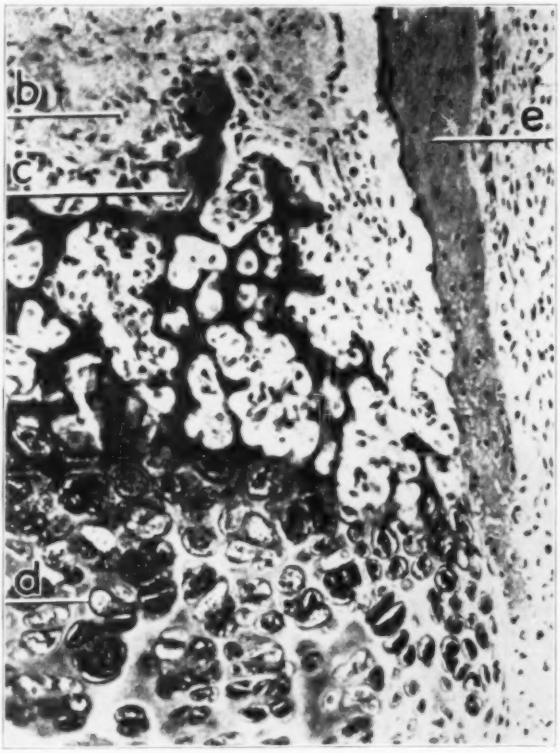

FIG. 15-B

Early stages of ossification in long bones: *a*, perichondrial bone (splint); *b*, primitive marrow; *c*, bone on calcified spicule of cartilage; *d*, proliferating cartilage; *e*, perichondrial bone. (Reproduced by permission of The C. V. Mosby Company, St. Louis, Missouri, from Bone and Bones: Fundamentals of Bone Biology, pp. 56 and 61, 1947, by J. P. Weinmann and Harry Sicher.)

shaft. Carey states that the stresses on the concave side are compressive and are not as intense as those on the convex side, which are tensile. He indicates that calcification of the cartilage matrix forms a central wedge-shaped zone with the narrow aspect directed toward the concavity of the femoral bar.

Undoubtedly a similar description would apply to the formation of the tibia or other long bones. Histological and embryological studies demonstrate that the developmental pattern of the limb bud in the human embryo is similar to that in the pig embryo.

Patten's *Human Embryology* illustrates a human embryo of thirty-nine millimeters (nine weeks) stained with alizarin and cleared to show the progress of ossification (Fig. 12). From the location of the ossification center in an embryo of 23.5 millimeters, it is evident that the lower portion of the central third of the tibia is the site of origin. The bent tibia can be clearly seen in this specimen and in all of the older similar specimens.

Geschickter and Copeland have an excellent illustration of a longitudinal section of the entire tibia of a human embryo, showing the early development of the ossification center in the mid-shaft of the tibia (Fig. 13). The typical constriction and pinching and hour-glass appearance of the cartilage rod at the site of ossification correspond to Carey's findings in the pig embryo.

Weinmann and Sicher illustrate the accepted concept of the development of endochondral bone in the metatarsal of a rabbit, demonstrating the degeneration of the chondrocytes and the cartilage matrix and the formation of perichondrial bone in the ossifying center. A splint or collar of bone pinching and contracting the degenerating cartilaginous anlage develops and acts as a support for this degenerating area undergoing destruction (Fig. 15-A). A higher magnification of the middle phalanx of a newborn infant illustrates this splint formation even better. One also sees the beginning invasion of the cartilage by richly vascularized tissue from the periosteum. The phalanx of a newborn infant illustrates a later stage of development (Fig. 15-B); here the perichondrial bone has formed a heavy collar and a primitive marrow center has been established.

It thus seems clear that embryologically there is a definite, well recognized acceleration of scleroblastemal tissue which progresses so rapidly that at the time of cartilage formation the muscles have developed and are active. Rotation of the limb bud occurs during this cartilaginous phase and during the phase of muscle activity. Carey does not consider the muscle action a cause of rotation, but believes that the deformation coincides with the resistance to femoral longitudinal growth. The senior author has demonstrated [1] that in arthrogryposis multiplex congenita rotation does not occur. The failure of rotation in this group, where the primary pathological condition seems to be a faulty development of the limb musculature, led him to the conclusion that rotation is a dynamic process controlled, in part at least, by the muscles. The fact that, as Carey has shown, the time of rotation and the development of muscle activity occur simultaneously cannot be coincidental. Therefore, we feel that in normal development both resistance to longitudinal growth and muscle activity produce the rotation.

The process of ossification of endochondral bone in the human embryo follows the pattern noted by Carey.

This is the pattern of normal development of the limb bud and its skeletal structure. Can we explain its abnormal development as noted in the characteristic features of congenital kyphoscoliotic tibia?

ABNORMAL DEVELOPMENT

The characteristic feature of the deformity, a constant mass of dense bone on the concave side of the bent tibia, has been observed by workers in experimental embryology.

Murray, in 1936, demonstrated just such a malformation in the femur of a chick developed as a chorio-allantoic graft after removal from the limb of a six-day embryo. His illustration also shows the femur of a normal fifteen-day chick embryo to demonstrate the normal development of the condyles, the head, and the trochanters (Fig. 14). The transplant shows the heavy mass of bone on the concave side of the femur with trabeculae radiating from the center of the curve, quite separate and distinct from the axial trabeculation of the normal portion of the femur. He discusses the trabecular direction in the bony mass from the standpoint of development in a bone bent by pressure, and schematically demonstrates that the direction should be parallel with the long axis. This seems to be true in bowing of the tibia in osteogenesis imperfecta, as observed by Weinmann and Sicher.

In a fractured and bent tibia of a chondrodystrophic chick embryo, Fell demonstrated a similar radial direction of trabeculae in the healing portion of the concave side and concluded that this was not adaptive (for then the direction of the trabeculae would be parallel to the tibia), but that the architecture is the consequence of the altered shape of the element, the large amount of bone formed, and the normal ossification pattern. The radiation architecture can be produced, according to Studitsky, by tensors set up in and below the periosteum by the growth of the cartilage in a newly hatched chick. Murray quotes Fell who demonstrated that these radiating bone trabeculae are from the inner sheath of bone surrounding the cartilage outward to the periosteum, so that they may be described as radiating from a hypothetical center in the middle of the diaphysis.

In a schematic figure demonstrating the space left between the perichondrium and the narrowed cartilage at the outer portion of the diaphysis, Fell showed that the subperiosteal space in the bent bone allows more extensive osteogenesis on the curved concave side, while the periosteum rests directly on the convex side, minimizing the space for bone formation.

The ossified mass on the concave side of the curve has been regarded by Caffey and others as a result of thickening of the cortex, with simultaneous thinning of the cortex on the convex side. It is clear, he states, that the cortical hypertrophy represents accretion due to failure of absorption of the cortex from within and does not represent subperiosteal accretion on the external cortical surface. With this concept we disagree. Several of our cases show definitely that this ossifying mass is not a normal thickening of the cortex; instead, the direction of the trabeculae diverges almost 90 degrees from the axial tibial trabeculations.

The denseness of the bony mass and the diminution of the medullary canal have the appearance of an aseptic infarct. Our first thought was that the abnormalities represented a developmental arrest of the primary cartilaginous bar at the time of earliest degeneration of the cartilage in the region destined to be the primary ossifying center; the primary marrow center also failed to form in this area. With this dense ossified mass present on the concave side, and with maintenance of continuity of periosteum on the convex side while growth from the epiphyseal ends progressed in a normal manner, bending of the bone would naturally occur.

PATHOGENESIS OF KYPHOSCOLIOTIC TIBIA AND ASSOCIATED DEFORMITIES

It seems clear, regardless of the etiology, that the development of the abnormalities in this condition must occur early in the cartilaginous phase or mesenchymal period. Agenesis of the fourth or fifth rays, of the fibula, or of other parts, and congenital amputations must be ascribed to the earliest phase of development.

The development of kyphoscoliotic deformity of the tibia clearly occurs in the primary center of ossification of the tibia and fibula, probably during the period of cartilage formation and muscle activity. The normal bending of the tibia is either accentuated or reversed. The increase in bending of the tibia, or the reverse of the normal bend which produces a posterior bowing, may be explained on the basis of an abnormal interference, such as that producing club-foot deformities in Bagg's experiments, in early embryonic life.

The fact that this does occur early in embryonic development seems perfectly clear. Both Bagg's and Warkany's studies show that the deformities in their abnormal mice and rats had their origin in lesions developing in the primitive cartilaginous stage.

The possibility of an hereditary or environmental fault of neurovascular origin must be given serious consideration in the explanation of this lesion. It may be wise to emphasize that the only invaders from the trunk into the otherwise self-sufficient limb bud are the nerves and vessels. Abnormal development or faulty timing of the neurovascular elements may be a definite factor. This is in keeping with Bean's suggestion that the only plausible explanation of the deformities occurring in the descendants of x-irradiated mice was a neurovascular disorder. The frequency of abnormal findings in the peripheral nerves of the limb in congenital deformities, as demonstrated by B. H. Moore [21], must be regarded as significant.

The persistence of the ossified mass on the concave side of the tibia is unlike the response of normal bone to the need for repair. It resembles rather an abnormal process which might be likened to an infarction. The density, the abnormal direction of the trabeculations, the persistence over many years of the abnormal ossification, and the delay in development of a normal marrow cavity are all characteristics opposed to the usual repair following trauma.

It would seem feasible to conjecture that, as the result of a neurovascular disturbance,

the primitive vascular channels allowed a bleb to form which was followed by a hematoma; this in turn would prove damaging to the ossification center of the tibia, particularly at the time of its origin. The constant location of the lesion at a level in the tibia corresponding to the primitive ossification center would strongly support this theory. Failure of formation of the primary medullary canal, inadequate collar formation, and bizarre ossification such as is characteristically seen in kyphoscoliotic tibia could then be reasonably anticipated. Likewise, the best explanation for the associated hypoplastic deformities of the fibula, the absence of one or more rays of the foot, congenital amputation, club-foot, and calcaneovalgus deformity of the feet would seem to be that they follow a process similar to that observed by Bagg in the descendants of x-irradiated mice.

Cutaneous changes, *café au lait* markings, and neurofibromatosis are closely related. Not infrequently the signs of neurofibromatosis appear years after birth in patients in whom *café au lait* markings had been noted early. These changes may emphasize the neurovascular basis of the abnormality.

The development of the abnormal tibia may then be summarized as follows:

1. Undifferentiated mesenchyme is present in the early limb bud.

2. Early condensation of the mesenchyme in the center of the limb bud forms the anlage for the skeletal framework.

3. This is followed by a period of rapid or accelerated growth of the scleroblastema into the cartilaginous skeleton.

4. Formation of muscle and muscle activity takes place in the cartilaginous phase.

5. Accelerated growth together with muscle activity produce forces which rotate the limb bud (invasion of the nerve supply and blood supply has preceded this phase, allowing muscle activity).

6. This is followed by bending of the tibia. Increased bending takes place, anterior or posterior in direction and abnormal in type, because of factors which occur about the fifth week of embryonic life and which interfere with the normal. This is the period in which abnormal neurovascular changes may occur. Although in hypoplasia resulting in absence of the foot, absence of the fibula, and of the fourth and fifth rays of the foot the abnormality may well occur at this time, it is quite possible that it may begin at an earlier period, through influences affecting the scleroblastemal phase.

7. The center of the cartilaginous skeleton fails to follow the usual pattern of bone formation, producing alterations in the primitive mesenchymal bar which in turn alter the type of rotation and bending of the tibia. The malossification, together with rapid growth and lessened elasticity, may act as a barrier to normal bend and rotation.

8. (a) The dense triangular bony mass on the concave side of the curved shaft of the tibia may have developed as the result of abnormal ossification of the mesenchymal bar. Continuity could, however, have been maintained by the normal periosteal cortical bone. This may be found in the bent tibia anteriorly or posteriorly, according to the direction of the bend in the deformed bone. Bone formation may be normal except in the scleroblastemal portion. This would account for the constant picture of the peculiar ossification on the concave side. It would explain the lines of separation at the arc of this abnormal ossification and the normal bone of the tibia proper in prepseudarthrosic and pseudarthrosic states. (b) There may be pinching of the mesenchymal tissue with abnormal bending; this would produce a separation of the periosteum on the concave side, the interval between becoming ossified with radially directed trabeculations, as demonstrated by Murray in embryological experiments. (c) Abnormal bending above may produce the increased space on the concave side to allow this unusual ossification.

9. The most logical conclusion from the embryological and histological evidence is that there is an interference with development, such as has been definitely demonstrated by Bagg in the descendants of x-irradiated mice. The accumulation of evidence of peripheral-nerve changes, vascular disorders, absence of development of parts, hypoplasia, and hyper-

plasia point to local change at the scleroblastemal or precartilaginous phase of development. The theory of neurovascular abnormality is based on the assumption that the original abnormality is in the embryonic origin of these structures and not later in the formed arteries or nerves. Inheritance, nutritional deficiency, or other factors may be the primary cause.

10. Growth from the epiphyseal ends continues normally in this condition as new cartilage is laid down to be replaced by bone.

Regardless of the method by which these deformities develop, the original fault must occur in the early phase of development of the limb bud prior to ossification of the skeleton. Then only can the characteristic features of the condition be explained.

It is quite possible that the neurovascular abnormality might produce damage only to soft tissues, producing an ischaemic lesion in the muscles of the extremity akin to that seen in arthrogryposis. Minimal damage to musculature might produce an alteration in development, such as that recently demonstrated by Bechtol and Mossman in a three-month foetus with club-foot.

TREATMENT

It would clearly seem advisable to make prevention of fracture the basic principle of early treatment in these cases. No attempts should be made to correct the deformity of the tibia, as growth from the epiphyseal ends will ultimately correct it. Correction of the varus or calcaneus of the foot is advisable. Protection by braces during early weight-bearing would seem advisable; it is suggested particularly in those cases showing cystic degeneration with a well defined differentiation between the dense bone mass on the concave side of the curve, and with minimal or no marrow space.

In the type of kyphoscoliotic tibia described by J. R. Moore [26] as prepseudarthrosis, there is certainly some justification for considering means for the prevention of the development of pseudarthrosis. We are convinced that the deformity should not be corrected. It would seem advisable, however, to consider in the more severe cases the use of dual onlay grafts on either side of the curve, extending well above and below the area of marked bone density into the normal bone of epiphyseal origin. Fracture may thus be prevented.

Spontaneous healing is the tendency, with regression of the deformity. Occasionally, osteotomy may be necessary for correction. The optimum policy for this procedure is probably to delay as much as possible so that the correction can be performed in normal bone from the distal tibial epiphysis.

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DISCUSSION

Dr. Clarence H. Heyman, Cleveland, Ohio: I wish to confine my discussion to congenital posterior angulation of the tibia, which I believe is a distinct clinical entity. I agree with Dr. Badgley that there are three types of congenital angulation of the tibia. We are all familiar with the first type; this consists in the congenital anterior angulations associated with spontaneous fracture and pseudarthrosis.

Figure A illustrates the second type of case. The deformity of the tibia in this group is associated with other abnormalities of development—chiefly, congenital absence of the fibula, congenital absence of some

of the bones of the foot, syndactylism, and perhaps congenital dislocation of the hip. There is no tendency to development of fracture and non-union. There is a severe and markedly resistant equinus deformity. The roentgenogram in Figure A was made when the patient was a baby. He was last seen at thirteen years of age. One foot has been amputated; we were able to correct the deformity in the other foot. His activities have been unrestricted.

FIG. A

J. S., at the age of thirteen months. X-rays show bilateral anterior angulation of the tibia, absence of the fibula, severe equinus deformity, and developmental abnormalities in the foot.

When the child was eleven years old, one foot had been amputated; the deformity of the other foot had been corrected and he seemed to be a normally active child. There has been no fracture of either tibia.

FIG. B

M. A. S., at eight months of age, April 6, 1941. There was severe posterior and medial bowing of the left tibia and fibula at the junction of the middle and lower thirds. The upper and lower tibial epiphyses appeared normal as compared with those on the right, although the left leg was shorter. Ossification appeared normal, except for a rather marked increase of density on the concave side of the curves.

Figure B illustrates a case of posterior angulation belonging to the third group, which is a distinct entity. In these cases the angulation is posterior and medial, and, as Dr. Badgley pointed out, there is a condensation of bone on the concave side of the curve. Figure C is a roentgenogram of the same patient seven years later. He had been treated only by a protective brace. At this time the tibia was straight and apparently normal. His activities had been unrestricted and he had not worn a brace for four years.

The characteristic features of this congenital posterior angulation are: (1) posterior and medial bowing of the tibia and fibula; (2) severe talipes calcaneus with tightening of the anterior muscles and weakness of the triceps surae; (3) shortening of the extremity confined, chiefly if not entirely, to the leg below the knee; (4) no detectable abnormality of the structure of the bone other than thickening of the bone cortex at the concave side of the curve; (5) no appreciable impairment, as determined by roentgenogram, of the proximal or distal tibial epiphyses; (6) no unusual tendency to fracture; (7) no associated abnormalities of development or pseudarthrosis; and, most important, (8) good prognosis under conservative treatment.

FIG. C

M. A. S. May 27, 1948, at the age of seven years. Ossification and alignment of the tibia and fibula were essentially normal following conservative treatment. The leg had been without protection for four years at the time these x-rays were made.

DR. J. R. MOORE, PHILADELPHIA, PENNSYLVANIA: Dr. Badgley has called to our attention two principal types of bowing noted in infancy, both of which may be classified as being congenital in origin. I would like to emphasize the fact that the principal difference between the bowing deformity in prepseudarthrosis which eventually leads to spontaneous fracture and the bowing deformity which spontaneously corrects itself lies in the appearance of the intramedullary cavity. In the prepseudarthrosis type of bowing, the medullary cavity is usually obliterated or becomes obliterated in the first year, after which the fracture occurs. A section of bone from the bowed area will show the primitive type of bone which does not have the characteristic Haversian canals and the lamination of mature bone. Those cases of bowing in which there is a medullary cavity present a thickening of the cortex on the concave side, presumably of periosteal origin. In these cases the medullary cavity never becomes obliterated. This type of deformity may spontaneously correct itself completely or it may end in residual bowing of varying degrees. It is upon this type that I have, on two occasions, performed a delayed osteotomy during infancy and have corrected the deformity. Healing occurred in a normal manner. I see no reason to wait for a spontaneous correction unless the bowing is of a relatively minor degree.

The prepseudarthrosis type of bowing appears to me to be a mesenchymal defect. The bone in this area lacks the ability to reach the status of mature bone.

DR. BADGLEY (closing): I would like to read my conclusions: Congenital kyphoscoliotic tibia is an entity frequently associated with other congenital malformations, chiefly hyperblastic in type, but occasionally hyperplastic. We found congenital malformation of other bones in patients with posterior bowing just as often as we did in those with anterior bowing. An explanation of the etiology of this lesion must therefore explain the associated deformities. We have demonstrated the characteristic features in twenty cases. The basic factor is an embryological alteration in bone growth at about the time of the formation of the ossifying center of the tibia and consequent interference with the normal development of this portion of the tibia. Increased bending of the tibia, secondary to degeneration of the cartilage, and poor ossification of the perichondrial splint or collar may occur. The subperiosteal portion, greater on the concave side, allows the formation of the ossifying mass. The primitive marrow cavity either fails to form properly or is diminished in extent, and the degree of diminution is the determining factor in whether or not pseudarthrosis will develop. The subperiosteal portion on the convex side of the curve is narrow, so that the bone mass formed here is minimal. This lesion of the tibia may be initiated by bleeding and later hemorrhage, as described by Bagg: a similar explanation holds for the genesis of the associated hyperplastic deformities.

(*Continued on page 404*)

GIANT-CELL TUMOR OF BONE*

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From the Campbell Foundation, Memphis

Progressive osteoclastoma or giant-cell tumor is easily mistaken for many other similar lesions which may be impregnated with giant cells. The differential diagnosis is often difficult. The problems of recurrence and metastatic changes are ever present and a satisfactory method of treatment has not yet been found.

The lesion was first described by Sir Astley Cooper in 1818. Lebert in 1845 gave a detailed delineation of the condition. Paget in 1853 wrote an excellent description of what he called a "myeloid tumor". Nélaton published a classical monograph in 1860 which remains a guiding treatise. Contemporary authors, among them Geschickter and Copeland, Jaffe and Lichtenstein, Bloodgood, Coley, and others have made many valuable contributions.

According to Geschickter and Copeland[14], "giant-cell tumor and the related lesion of bone cyst are the result of an abnormal hyperplasia of osteoclasts preceded by a normal stage in which osteoclastic proliferation is taking place as a phase in the histogenesis of intracartilaginous bone".

Various lesions may contain many giant cells, but true giant-cell tumors of bone are rare. The forty-one cases in our study were taken from the records of the Campbell Clinic over a period of twenty years; this is an average of two per year. During the same period of twenty years, 211 patients with sarcoma of bone and forty-three patients with solitary bone cyst were treated. Sir Harry Platt states that these tumors are seen in England on the average of about one a year for each hospital.

Giant-cell tumors occur essentially in early adulthood; in most series the incidence is highest in the third decade. The average age in our series was 28.4 years, while the average age in the series of forty-six solitary bone cysts reported by Stewart and Hamel was fifteen years. There is almost no predilection for either sex in giant-cell tumor, while our records of bone cyst show that the ratio of males to females is three to one.

Almost all bones of the body have been involved by this tumor. According to Geschickter and Copeland[14], however, it occurs only in bones which have been formed from cartilage; this excludes primarily parts of the calvarium. The majority are found in the distal end of the femur, proximal end of the tibia, distal portion of the radius, and proximal portion of the humerus. In the Memorial Hospital series reported by Coley[5] sixty-six out of 124 tumors occurred about the knee.

CLINICAL FEATURES

History

The first symptom is usually pain followed by swelling or tumefaction, but effusion into the adjacent joints or a pathological fracture may be the initial finding. Approximately 50 per cent. of our patients gave a history of trauma.

The symptoms are usually noticed six to twenty-four months before the patient consults a physician. In our series, the average time was fifteen months. Pain, the driving symptom, is most severe when the involved portion of the body is active. Night pain is noticed frequently, but it is not of the distressing nature associated with sarcoma.

Examination

Moderate to severe tenderness is present over the involved area, and tumefaction

* Read at the Annual Meeting of The American Academy of Orthopaedic Surgeons, Chicago, Illinois, February 1, 1951.

is palpable if the location is superficial. A definite area of demarcation at the juncture with normal bone is common; this is in contrast to sarcoma, which presents a fusiform firm swelling with its edges sloping smoothly into the adjacent bone. On palpation the paper-thin cortex may give the sensation of "egg-shell" cracking, or there may be a firm fibrous doughy consistency. Frequently there is hyperaemia with increase in the local temperature.

Roentgenographic Appearance

The roentgenographic picture of a giant-cell tumor is that of a circumscribed osteolytic process eccentrically placed in the epiphysis of a long bone. The thin bony shell is often fractured or perforated.

Willis described a specimen in the Hunterian Museum of the Royal College of Surgeons of England which demonstrates a typical giant-cell tumor growing in the metaphysis and just beginning to cross the epiphyseal plate. He believes that, if a giant-cell tumor appears in the bone before this epiphyseal line is closed, it will be in the metaphysis.

Two lesions in our series confirmed this; one of these occurred in the upper femoral metaphysis in a ten-year-old patient, the other, in the distal end of the radius. The lesion in the radius was removed when the patient was sixteen years old.

The cortex over the tumor is thinned and expanded by the cellular growth. The tumor does not invade the articular cartilage. Extension into the shaft is usually limited by a thin area of sclerotic bone and fibrous tissue. There is typically, as in bone cyst, no periosteal reaction unless fracture has occurred. Bloodgood [1,2] was the first to state that rupture of the cortex could and frequently did occur in benign tumors. In our series, rupture of this shell was noted in half of the cases. Trabeculations or ridges dividing the mass into compartments also are often seen.

Differential diagnosis is often difficult; osteolytic osteogenic sarcomata, solitary myelomata, enchondromata, benign chondroblastomata, so-called giant-cell variants, and hyperparathyroidism with cystic lesions, all show similar characteristics. Differentiation between this lesion and a bone cyst by roentgenogram may be difficult, especially in the younger age group. The relatively rapidly growing bone cysts in the active phase—that is, when they are adjacent to the epiphyseal plate—may have many of the characteristics of a giant-cell tumor. At biopsy, these cysts may show multiple giant cells scattered through a fibrous-tissue stroma, but the stroma is one of the major pathological differences between solitary bone cysts and giant-cell tumor.

Changus recently demonstrated, in a limited number of cases, a histochemical method of differential diagnosis. This is based on the fact that the giant cells and stromal cells of giant-cell tumor contain acid phosphatase and no alkaline phosphatase, while in bone cyst and fibrous dysplasia the few giant cells present may contain acid phosphatase and the stromal cells show only alkaline phosphatase.

Gross Pathology

The classical description of the gross pathology emphasizes advanced necrosis, cystic degeneration, large blood spaces, and diffuse staining by degenerated blood pigment. As pointed out by Jaffe and Lichtenstein [21], however, this classic appearance is that found in old or neglected tumors. Currently most of the tumors are diagnosed early and therefore have a more viable appearance. Sections reveal a surface which is grey to reddish brown in color and which is filled with soft friable material and hemorrhagic areas. Patches of yellow, orange, and amber necrosis or even liquefaction may be present. A few of these tumors may show frank pulsation at operation; in our series there was one such lesion occurring in the proximal end of the femur. When a needle was inserted into the mass, blood squirted in rhythm with the pulse beat; but, once the contents of the shell had been evacuated, hemorrhage ceased.

Microscopic Appearance

The tumor consists of a network of stroma and giant cells apparently growing without support in blood-filled spaces. Bone is rarely seen in the tumor except for portions of bone which have been incompletely absorbed from the host. The stromal cells predominate and are of two types, rounded and spindle, but there are variations in shape and size of this same cell type. The cytoplasm is moderately dark, slightly bluish, and poorly delineated. Even in benign lesions, mitotic figures are occasionally seen. The giant cells are large, conspicuous conglomerations of cytoplasm, fifty to 100 micra in diameter, and there are, characteristically, twenty to thirty per low-power field. Their cytoplasm is slightly more acidophilic than that of the stromal cells and is often ill defined. They may contain from three to 200 nuclei of the stromal-cell type.

It has been noted that, the smaller the giant cells, the greater the tendency toward malignancy. In several of our sections, we saw that near the advancing edge of the tumor, where bone was being eroded or pushed back by the proliferating tumor cells, the giant cells were consistently small, many in number, and sparsely nucleated. In the more central portion of the tumor the giant cells were larger, contained many nuclei, and appeared more sluggish or inactive.

GIANT-CELL TUMOR VARIANTS

The authors' attitude toward these conditions has been patterned after that of Jaffe and his associates[17-21]. They believe that there is only one specific entity which can be called a giant-cell tumor. Each variant is either a giant-cell tumor modified by treatment or an entirely separate and different entity. For instance, they hold that a spindle-cell variant on close examination frequently proves to be a medullary fibroma. Similarly the cartilaginous variant may be a chondroblastoma. They consider epulis, brown tumors of hyperparathyroidism, and tendon-sheath xanthomata to be entirely different lesions. This concept simplifies the study of giant-cell tumors by differentiating them from lesions in which the presence of giant cells is the chief claim to kinship.

PROGNOSIS

Giant-cell tumors are undoubtedly neoplasms and as such can be expected to recur in sites where extirpation has been incomplete, and perhaps to undergo malignant changes. The lesion was first described as a myeloid sarcoma and was considered malignant. The benign character was gradually recognized, but amputation was still the treatment of choice at the turn of the century. Bloodgood[1,2] in 1923 and 1924 reported a total of 177 cases; there were no deaths in his series. He concluded that true giant-cell tumors would not metastasize and thus established the term "benign giant-cell tumor".

Repeatedly reports have appeared in the literature of apparently benign giant-cell tumors which ran a malignant course. This is a very difficult claim to substantiate. Reviewing pathologists may question the benign character of the original tumor or the malignant appearance of the recurrence. Even metastases are subject to suspicion. A sarcomatous node in a lung may not necessarily be derived from a giant-cell tumor which was amputated several years before. In one of our cases, a reported metastatic nodule in the lung was later proved to be tuberculosis. For these reasons, very few of the earlier reports of malignant giant-cell tumor have escaped question. In recent years, however, a small number of cases have been reported which appear to leave little doubt that a patient whose original lesion was a benign giant-cell tumor has died of metastases.

Some of these metastases contain giant cells, while their stroma is that of an anaplastic sarcoma. This has raised another question: Have the cells of the tumor gradually become more and more anaplastic or has a focus of sarcoma appeared within the original tumor but independent of it? Geschickter and Copeland hold strongly to the latter view,

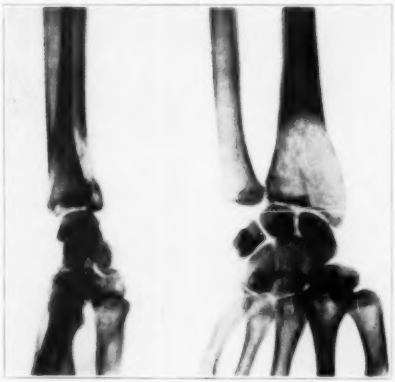

FIG. 1-A

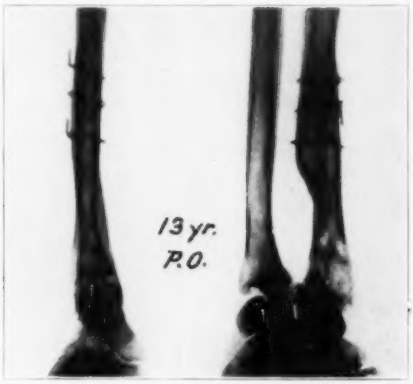

FIG. 1-B

Case 10, Mrs. J. O. Y. A giant-cell tumor was removed and the distal end of the radius was resected and replaced by the proximal end of the fibula. Thirteen-year follow-up.

but other present-day authors believe that all degrees of malignancy may be found. Meyerding [25], in reviewing 124 cases, seen at the Mayo Clinic from 1916 to 1940 inclusive recognized twenty-three instances of such degrees of malignancy and labeled them "malignant giant-cell sarcoma". Platt speaks of "malicious" giant-cell tumors. Ewing attempted to classify giant-cell tumors on the basis of clinical, roentgenographic, and microscopic findings in order to determine in advance their propensity to recurrence or malignant degeneration.

The most recent attempt along this line was that of Jaffe, Lichtenstein, and Portis who, in 1942, set up a series of three grades based entirely on the micropathology of the stromal cells. We have attempted to grade the cases in our group by these criteria.

Grade I represents the typical giant-cell tumor. The stromal cells are essentially of the same size and shape, and there is little difference in their morphology.

Grade II represents all degrees of atypia which are not frankly malignant. The stromal cells are more closely packed and their cytoplasm and nuclei vary in size, shape,

FIG. 2-A

Case 6, Mrs. C. F. S. After removal of a giant-cell tumor, the distal end of the radius was resected and replaced by the proximal end of the fibula. Follow-up period was nine years and eight months.

FIG. 2-B

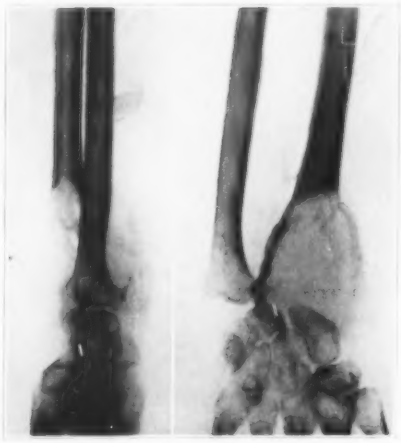

FIG. 3-A

FIG. 3-B

Case 38, Mrs. G. C. B. A giant-cell tumor was removed and the distal end of the radius was resected and was replaced by the proximal end of the fibula. Follow-up period was seven years.

and density. Mitotic figures are not frequent, but a few bizarre figures are present. The giant cells may be similar in size and shape to those of Grade I, but their nuclei will reflect the atypia of the stromal cell. Tumors of this grade are still benign but are more likely to recur or to undergo malignant degeneration.

Grade III comprises the frankly malignant lesions. This is called a malignant giant-cell sarcoma by some authors and malignant variant by others.

SURGICAL TREATMENT

The ideal of successful treatment is complete ablation of the tumor cells from the body. This can be obtained by amputation, but a less deforming type of therapy is desirable. Bloodgood [2] led the way toward a less radical approach when he reported ninety-three lesions which were curetted; there were only eighteen recurrences. It was he who laid down the principles of thorough curettage followed by chemical cauterization.

Resection

If practical, resection is the treatment of choice; this is being used more and more

FIG. 4-A

FIG. 4-B

Case 7, Mrs. B. N. A giant-cell tumor of the anterolateral aspect of the distal end of the tibia was removed; the tibia was curetted and the space was filled with autogenous bone chips. Follow-up was for ten years.

TABLE I

RESULTS OF TREATMENT IN THIRTY-FOUR CASES

Type of Treatment	No. of Cases	No Recurrence after Five Years	Progress toward Cure	Recurrence	No Follow-up
Amputation	5	2	2		1
Excision	9	3	2	2	2
Curettage (with or without cauterization)	6	2		2	2
Curettage and bone graft	14	4	5	5	
Total	34	11	9	9	5

as new methods of replacing the excised bones are devised. The writers have had four patients in whom the distal end of the radius was replaced by the proximal end of the fibula. One of these operations was performed less than a year ago. The other patients, however, have been followed from seven to thirteen years, and all have satisfactory wrist and hand function.

CASE 10, Mrs. J. O. Y. (Figs. 1-A and 1-B). Five years after surgery, this patient had a recurrence of the tumor in the soft tissues between the radius and the ulna. The mass was re-excised and roentgen treatments were given. Thirteen years after the first surgical procedure, she had no sign of recurrence and had good function in the wrist and hand.

CASE 6, Mrs. C. F. S. (Figs. 2-A and 2-B). In this patient the distal portion of the radius was resected and was replaced by the proximal end of the fibula. Nine years after surgery she had no sign of recurrence; she was doing all of her own housework and had a good range of motion in the wrist, with a good result.

CASE 38, Mrs. G. C. B. (Fig. 3). In this patient resection of the radius and transplantation of the proximal end of the fibula were performed. Seven years after surgery she had moderate limitation of flexion of her wrist, very little practical disability, and was well pleased with the function. The fibula from the opposite leg should be used and more flexion of the wrist will be allowed.

It is interesting to note that Higinbotham and Coley achieved similar results by substituting two tibial grafts for the distal end of the radius.

Curettage

The second method of treatment, curettage, is usually followed by chemical cauter-

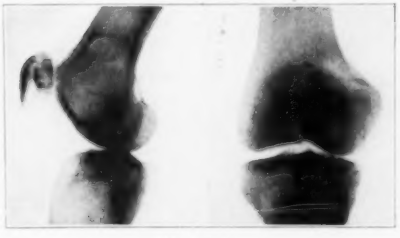

FIG. 5-A

FIG. 5-B

Case 13, Mrs. W. L. G. A giant-cell tumor of the medial femoral condyle was removed; the condyle was resected and was replaced by a whole-thickness iliac-bone graft and autogenous chips. The follow-up period was six years.

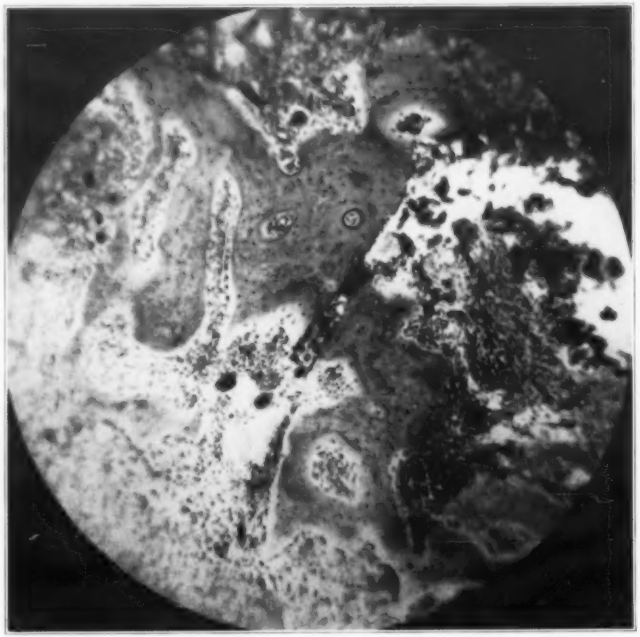

FIG. 6

Case 10. Mrs. J. O. Y. Photomicrograph (× 100) showing small giant cells from the advancing edge of a tumor entering normal tissue and immediately enlarging.

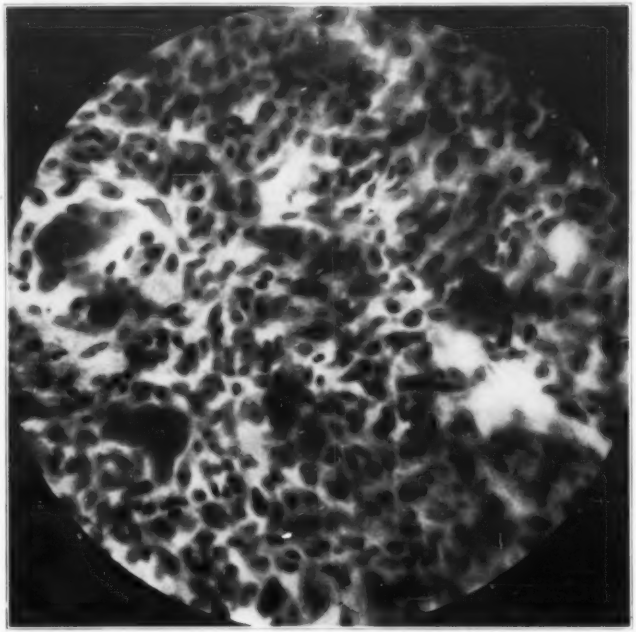

FIG. 7

Case 3. Mrs. S. A. McM. Section from a biopsy, illustrating a typical Grade II tumor.

ization to assist in removal of the tumor cells. In recent years, filling the cavity with autogenous grafts from the ilium or with grafts from the bone bank has become a popular procedure. The combination of these procedures produces better results than curettage alone.

CASE 7, Mrs. B. N. (Figs. 4-A and 4-B). The roentgenograms show the result ten years after treatment of a giant-cell tumor of the distal end of the tibia by curettage and packing with bone chips. When last seen the patient was walking without a limp and without pain, but there was moderate restriction of motion associated with early arthritic changes.

CASE 13, Mrs. W. L. G. (Figs. 5-A and 5-B). In this case a complete removal of the medial femoral condyle with replacement by iliac bone was done. The lesion extended to the articular cartilage but did not invade the joint. It was limited on the shaft side by a thin area of sclerosis. Six years later the knee was stable and motion was from 180 to 60 degrees, and without pain. The patient was on her feet eight hours or more a day. There was mild crepitus on motion with some osteo-arthritic changes, but function was good.

In 1945, Meyerding [26] reported a remarkable series of forty patients treated by this method with only one recurrence. No other writers have reported such excellent results.

RADIATION THERAPY

The wisdom of roentgen or radium therapy for any benign tumor which can be handled by other means is questionable. The problem of overdosage is present, although it is not a dangerous factor in modern therapy. A far more serious problem is the likelihood of late malignant degeneration. There is ample evidence, both experimental and clinical, that exposure to roentgen irradiation can produce sarcomatous changes in a previously benign tumor or even in normal tissue.

Hatcher, in 1945, collected reports of twenty-four such occurrences and added three of his own. Cahan and his collaborators, in 1948, listed eleven cases from the Memorial Hospital files. Of these, nine were giant-cell tumors. Nearly all writers advocating primary roentgen therapy report a few examples of malignant change. Leucutia and Cook in a recent article developed a theory which they attempted to support by a thorough review of the literature. It was their opinion that controlled roentgen therapy is no more likely to produce sarcomatous changes in a giant-cell tumor than is surgery. Nonetheless, the generally accepted view is that there is increased danger of this unwelcome complication. To this must be added the fact that roentgen therapy without adequate biopsy is based on a dangerously presumptive diagnosis. Most authorities, therefore, reserve this form of treatment for lesions which are inaccessible to surgery.

Two points are paramount in considering roentgen therapy. In the first place, it has frequently been reported that there is a period following treatment during which the tumor appears to increase in size and activity. The observer must not be made panicky by this phenomenon and let himself be led into giving further unnecessary treatment. Secondly, a giant-cell tumor which has been subjected to radiation heals by fibrosis and gradual ossification within its mass. There is little change in the cortex. On the other hand, a tumor which has been curetted heals first by condensation of the cortex. Thus x-irradiated bone is subject to the hazard of pathological fracture for a considerably longer period than it would be if the tumor had been extirpated surgically.

OTHER METHODS OF TREATMENT

Johnson and Lyford, in 1945, reported successful treatment of five cases of giant-cell tumor of the distal end of the femur by telescoping the shaft into the cavity of the curetted bone. No grafts were used. They obtained solid healing, but the period of time required was a little longer than for a supracondylar fracture. Excellent function of the joint and little disability were reported, although shortening of the extremity ranged from three-fourths of an inch to three inches.

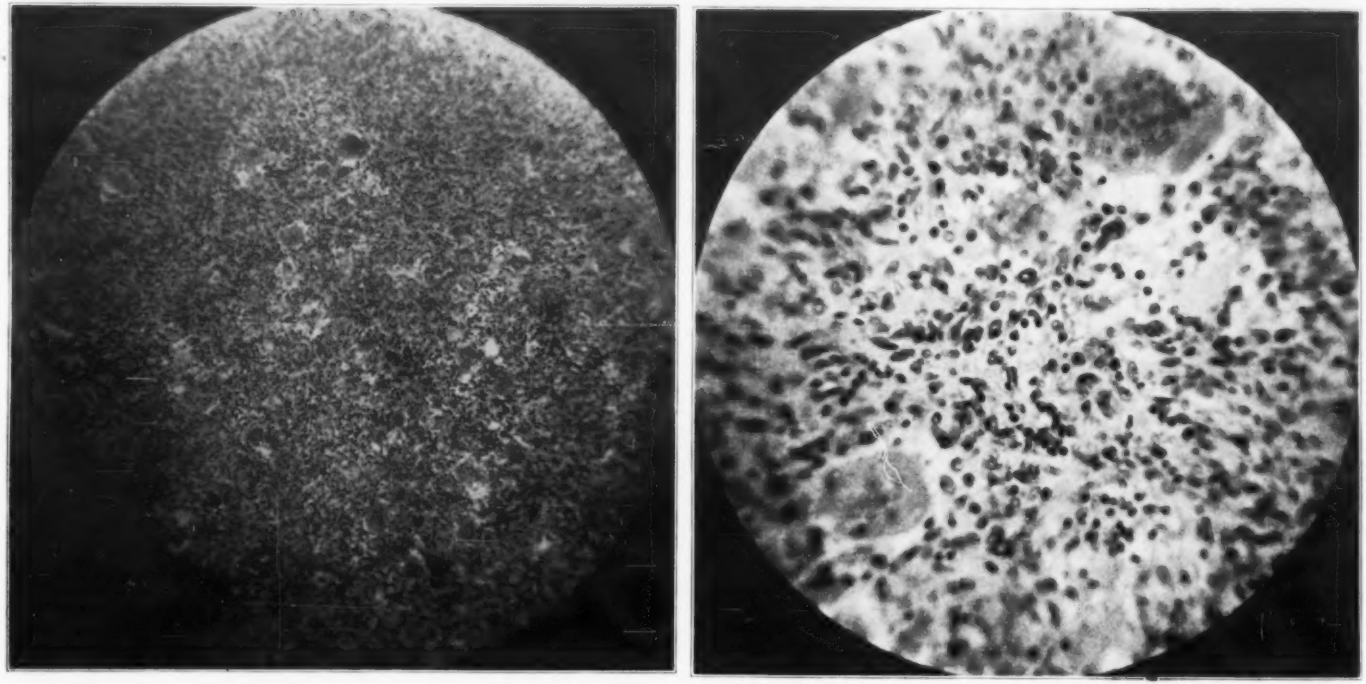

FIG. 8-A

FIG. 8-B

Fig. 8-A (low-power photomicrograph, × 100) and Fig. 8-B (high-power photomicrograph, × 430): Case 27, Mrs. H. H.: Showing typical giant cells but atypical stroma. The tumor was diagnosed as a giant-cell tumor.

REVIEW OF CASES

The series reported consists of forty-one cases from the Campbell Clinic files for all of which there are adequate records, roentgenograms, and microscopic sections. All presented the typical micropathology of giant-cell tumor, but seven were somewhat atypical from other points of view and for this reason were omitted from the final tabulation.

Table I shows the results of primary therapy in the remaining thirty-four cases. All patients have been listed as cured who were alive and who showed no evidence of recurrence at the end of five years. Those listed as "progress toward cure" showed no clinical or roentgenographic evidence of recurrence when last examined, more than one year but less than five years after treatment.

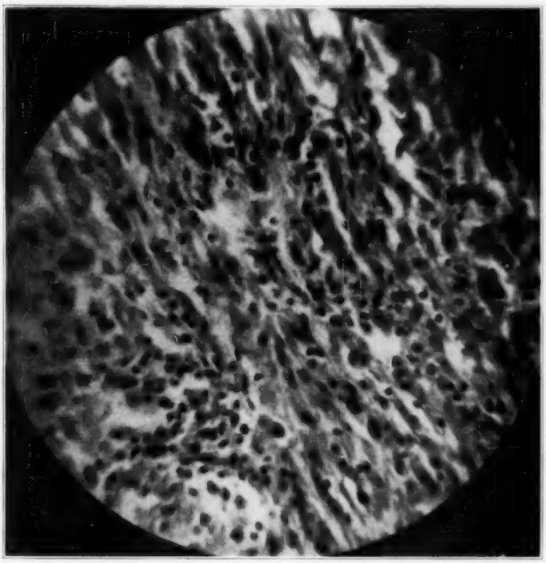

FIG. 8-C

(Photomicrograph, × 400.) After recurrence and amputation, sections showed this tumor to be a highly malignant anaplastic sarcoma. The malignant nature of this lesion should have been evident from the first section.

Results

Five patients had primary amputation. One was not followed, but there were no recurrences among the other four.

Nine patients were treated by excision or resection of the involved area of bone. Three of these were well at the end of five years; two showed progress toward cure. Two patients had recurrences, and two have been followed less than a year.

Six patients were treated by curettage. All but two of these had cauterization with phenol and alcohol. In this group two were cured, two showed recurrences, and two were not followed.

Fourteen patients had curettage, cauterization with phenol and alcohol, and finally packing of the cavity with bone chips. Nine were considered cured or progressing toward cure and five had recurrences. In the earlier cases, the bone grafts and chips were obtained from the adjacent cortical bone. Autogenous iliac or bone-bank bone is now being used; consequently, the supply of bone is more abundant and the results are consistently better.

Thus, of the thirty-four patients, eleven appeared to be cured after five or more years, nine were progressing toward cure, nine had recurrences, and five were not followed.

There were twenty-nine patients treated conservatively,—that is, by methods other than amputation. Of these, nine had recurrences, an incidence of approximately one in three.

From the standpoint of recurrence, the results of amputation were classified as good.

The average time between treatment and recurrence was thirty-one months, with a range of one month to six years.

The following two cases illustrate the fatal outcome of a malignant tumor.

CASE 3, Mrs. S. A. McM. There was exuberant recurrence after resection of the head and neck of the

TABLE II

REVIEW OF CASES WITH RECURRENCES

Case No.	Initials	Sex	Original Site	Original Treatment	Time of Recurrence	Treatment of Recurrence	Final Result
3	S.H.M.	F	Proximal portion of femur	Resection	1 mo.	None	Died
5	J.M.	M	Distal portion of femur	Curettage and bone chips	14 mos.	Amputation	Good
7	H.F.O.	F	Distal portion of tibia	Curettage and bone chips	17 mos.	Curettage and roentgen therapy	Good
10	J.O.Y.	F	Distal portion of radius	Resection	6 yrs.	Soft-tissue excision and roentgen therapy	Good
12	G.D.C.	M	Distal portion of femur	Curettage	5½ yrs.	Curettage and bone chips	Good
14	O.W.H.	M	Proximal portion of tibia	Curettage and bone chips	6 yrs.	Amputation	Good
19	L.H.	M	Proximal portion of femur	Curettage and bone chips	19 mos.	Roentgen therapy	Poor
26	J.S.	M	Distal portion of femur	Curettage and bone chips	20 mos.	Curettage and bone chips	Not followed
27	M.H.	F	Distal portion of femur	Curettage and bone chips	6 mos.	Curettage and bone chips	Died

femur. The micropathology showed a "malicious tumor", corresponding to Jaffe and Lichtenstein's Grade II. Figure 7 illustrates a section from the biopsy which shows what we consider to be typical of this kind of tumor. This patient grew rapidly worse and died. There is some doubt whether she died of metastases, for a rather severe secondary infection developed in a fungating tumor at the site of surgery. No autopsy was obtained.

CASE 27, Mrs. H. H. This patient was a female, aged twenty-eight, with involvement of the distal end of the femur. She had experienced a dull pain in the knee for about twelve months prior to admission. The roentgenograms revealed a destructive lesion involving the distal epiphyseal area of the right femur. Surgical treatment consisted of curettage and grafting with iliac-bone chips. Micropathologically, the sections revealed a "giant-cell tumor" with typical giant cells but atypical stroma (Fig. 8-A). The diagnosis of giant-cell tumor was confirmed by two pathologists. After recurrence of the tumor and amputation, the sections revealed progressively malignant changes which, on closer study, showed this to be a highly malignant anaplastic sarcoma (Fig. 8-C). The patient died of widespread metastases just a year after her first operation. Review of the original biopsy with more careful scrutiny revealed that the malignant nature of this tumor should have been recognized at that time. This patient had not received roentgen therapy.

An interesting finding in this case was a white-blood-cell count ranging as high as 86,000. Hematologically, this was a leukemoid reaction; presumably it amounted to an over-reaction of the bone marrow to massive invasion by tumor metastases. It is interesting to speculate, however, whether blood-forming elements might have appeared within the metastases. Theoretically, this is possible.

An attempt was made, from examination of the recurrent tumors, to find some factor or factors which might explain this undesirable event or at least allow prediction of its occurrence.

TABLE III

POSSIBLE CAUSES OF RECURRENCE

Initials	Case	Cortex Broken	Time of Onset (*Months*)	Pathological Fracture	Jaffe and Lichtenstein's Grade	Average No. of Nuclei per Giant Cell
S.H.M.	3	Yes	17	Yes	II	12
J.M.	5	No	6	No	I	5
H.F.O.	7	No	12	No	I	15
J.O.Y.	10	Yes	4	No	I	16
G.D.C.	12	Yes	2	No	I	8
O.W.H.	14	Not reported	5	No	I	50
L.H.	19	Yes	15	No	I	25
J.S.	26	No	8	No	I	18
M.H.	27	No	12	No	II	5
Average in this Group		50 per cent.	11.2	11 per cent.	22 per cent. in Grade II	17.1
Average in Series		50 per cent.	15	18 per cent.	4.3 per cent. in Grade II	24.0

Table III lists some of the factors which have been mentioned in the literature as being important.

Broken Cortex

Geschickter and Copeland feel that this is of considerable significance. It may indicate greater activity within the tumor, or it may increase the difficulty of removing all the tumor cells. In our series, the cortex was broken, as noted by roentgenographic examination or reported at the time of surgery, in 50 per cent. of all the cases, with or without recurrence.

Time of Onset

Rapid onset suggests an active tumor. Analysis of the time between the onset of symptoms and beginning of treatment in this series yielded no significant difference between cases with and cases without recurrences.

Grading

Jaffe and his co-workers [19], as stated previously, believe that a difference in the microscopic appearance of the stromal cells will indicate potential recurrence or malignancy. None of our cases were classified as Grade III on the basis of the first sections, but three were classified as Grade II. Of the latter, two patients died, apparently of malignancy. This grading may be of questionable value in predicting the likelihood of recurrence, but it is useful in that Grade II and Grade III give the pathologist convenient categories by which he may indicate the degree of his suspicion of the tumor.

Size of Giant Cells and Number of Nuclei

The number of nuclei in a cell is a good index of its size. The nuclei in numerous giant cells in different fields were counted and the average was determined for each case. There was a significant difference, as shown in Table III, between the average number of nuclei in the giant cells of the patients with recurrences and those without recurrences. In several slides in this series it was found that giant cells near the growing, advancing edge of the tumor tend to be smaller than those within the tumor mass (Fig. 6). Here small, apparently active cells are seen in an area of perforation of the bone. Whether their size is an index to their activity or their immaturity is the question.

TABLE IV

LATE FUNCTIONAL RESULTS

Excellent	4
Good	5
Fair	2
Poor (two died and one had resection of the head and neck of femur)	3
Amputations (no recurrences)	6
Total	20

Other Factors

Such factors as the size of the blood spaces, the amount of fibrous tissue, the density and morphology of the stromal cells, and the pattern of their distribution were considered but contributed little. We believe that accurate diagnosis, followed by thorough ablation of the tumor cells and adequate bone replacement determines the outcome of treatment.

LATE FUNCTIONAL RESULTS

Late functional results of treatment were determined in twenty cases from the typical series which were followed five years or more or whose final fate was established by amputation or death.

Results were considered to be *excellent* if there was no disability and no evidence of recurrence.

Results were considered to be *good* if there was little disability, only slight pain, with or without arthritic change in the adjacent joints, and no evidence of recurrence.

A grading of *fair* indicates partial disability, with pain as a definite complaint, and considerable arthritic changes in the joint, but no evidence of recurrence.

A grading of *poor* includes those patients who were completely disabled.

Of the twenty patients for whom late results were obtained, there were four with excellent results, six with amputations, five with good, two with fair, and three with poor results.

The six patients on whom amputations were performed have shown no evidence of recurrence.

The poor results included one patient totally disabled because of pain in the hip joint, and two deaths.

CONCLUSIONS

True giant-cell tumors are quite rare. Solitary bone cysts occur with about the same frequency, while sarcomata of bone are found five times as often as either.

We agree with Geschickter and Copeland[14] that there is a close clinical kinship between giant-cell tumor and solitary bone cyst, and that they probably have a common origin.

Giant-cell tumors are neoplasms and as such can be expected to recur in sites of incomplete extirpation. Moreover, they may undergo malignant changes, either through trauma or as a result of inadequate treatment.

The number and size of the giant cells, together with the number of nuclei per cell, furnish the best criterion for determining the prognosis. The small, sparsely nucleated giant cells with a tendency for collection of many cells in each high-powered field indicate more activity and rapid growth. These tumors have a greater tendency to recur or become malignant.

X-irradiation should be reserved for those lesions inaccessible to surgery. The danger of incomplete cures, recurrence, and of an overdosage of roentgen rays are not as important as the hazard of late sarcomatous changes.

Resection of the involved portion of a bone where feasible is the treatment of choice.

The distal portion of the radius can be supplanted successfully by the proximal end of the fibula. The femoral condyle can be replaced by a section from the ilium.

If resection is not practical, the next best method of treatment is thorough curettage, with or without cauterization, together with multiple bone grafts or chips to fill the cavity. The most important single factor in this method applies to the treatment of solitary bone cyst as well as giant-cell tumor: this is thorough curettage, breaking through and destroying the limiting wall and thus opening into the normal cancellous bone of the shaft. Bone chips or grafts should be inserted when large defects are created.

The so-called giant-cell variants in most instances are probably separate and distinct pathological lesions resembling this tumor only through the presence of giant cells.

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THORN-INDUCED "TUMORS" OF BONE*

BY DONALD J. MAYLAHN, M.D., CHICAGO, ILLINOIS

Organic material, such as the thorns of plants, when present in or near a bone, can produce a pathological reaction, the roentgenographic appearance of which may resemble bone tumor. This possibility should be considered in the differential diagnosis of bone neoplasms.

Many articles can be found in the recent literature on reaction of bone to metal; a review of the literature of the past thirty years, however, yields no reference to bone reaction to organic foreign material. Breinlinger[1], in a recent review of the literature, did find reports of experimentally induced new-bone formation around foreign bodies; the materials used were chosen for their non-toxic or non-irritating properties or because of characteristics favorable to the production of bone. On the other hand, reports on the reaction of bone to toxic and irritating organic material cannot be found.

Fig. 1

Case I. A. V. Showing cortical erosion of the bases of the fourth and fifth metacarpals.

* Read before the Chicago Orthopaedic Society, May 11, 1951.

Plant thorns in or near bone can produce either an osteolytic or an osteoblastic reaction, or a combination of these. It has been possible to collect three cases in which one or both of these reactions have occurred. It is interesting that, although the introduction of organic material (such as catgut) in or near bones is not infrequent, a gross reaction in bone has been observed, to the author's knowledge, only to thorns. One can only speculate on the nature of the toxic substance responsible for these changes, and experimental investigation will have to be carried out to ascertain whether or not this type of bone reaction is unique to thorns.

The principal factor in making the diagnosis of bone reaction to an organic foreign particle is the degree of the physician's suspicion; without this, a history of trauma is very often overlooked or minimized. As these bodies are radiolucent, the diagnosis can be verified only by biopsy.

As to treatment, in the three cases reported removal of the organic foreign body has resulted in cure.

CASE REPORTS

CASE 1.* A. V., age seven, Mexican, male, was first seen on June 27, 1949, after a fall on the outstretched right hand on the same day. Physical examination revealed a small abrasion on the hypothenar eminence accompanied by swelling and tenderness at the base of the fourth metacarpal. Clinically the condition resembled a greenstick fracture at the base of the fourth metacarpal. Roentgenograms made on that day, however, revealed no evidence of a fracture. After thorough cleansing of the wound, a plaster splint was applied.

Since tenderness persisted, a greenstick fracture was suspected and roentgenograms were again made on July 11, 1949. These gave no evidence of fracture. A splint was reapplied and was allowed to remain in place until August 1. On this date examination revealed a mass in the palm of the hand which was interpreted as exuberant callus until roentgenograms (Fig. 1) revealed a punched-out area of cortical erosion at the bases of the fourth and fifth metacarpals. The diagnostic possibilities now considered were a neoplasm or a lytic granuloma. The tuberculin test, blood counts, sedimentation rate, and the serological reactions on August 2 were within normal limits. The patient was treated with 0.5 cubic centimeter of long-acting penicillin for ten days with only slight improvement. It was then decided that a biopsy was necessary.

FIG. 2

Case 2. M. S. Showing osteolytic lesion of the distal end of the first metacarpal; there is no reactive bone formation.

On August 18, through a short transverse incision on the dorsum of the hand, the space between the fourth and fifth metacarpals was exposed. After the extensor aponeurosis had been opened, one could see a small black object. This was extracted and found to be a yucca thorn, three centimeters long. After the thorn had been extracted, about two cubic centimeters of purulent material oozed from the wound. It was sent to the laboratory for culture. Following thorough saline irrigation, the wound was closed tightly.

Bacteriological study revealed a gram-positive bacillus.

The child received penicillin for ten days. The wound healed *per primam*.

Roentgenograms made six months after removal of the thorn showed complete restitution of the bone, and clinical examination yielded normal findings.

CASE 2.** M. S., female, fifty-eight. In May 1946 the patient sustained a puncture wound from a rose thorn on the palm of the right hand proximal to the head of the fifth metacarpal. The wound healed un-

* Through the courtesy of Morton H. Leonard, M.D., El Paso, Texas.
** Through the courtesy of Herbert E. Hipps, M.D., Waco, Texas.

eventfully, but lancinating pain across the palm of the hand, when the patient attempted to grasp, persisted. In September 1946, pain at the metacarpophalangeal joint of the thumb became severe and was followed by swelling and abscess formation. Surgical drainage was performed, but a sinus persisted.

Examination on May 12, 1948, revealed a round elevated draining sinus, 0.5 centimeter in diameter, on the dorsum of the first interdigital web of the right hand, accompanied by thickening, swelling, and tenderness with limitation of motion of the metacarpophalangeal joint of the thumb. A healed puncture wound just proximal to the head of the fifth metacarpal was noted.

Roentgenograms (Fig. 2) demonstrated an osteolytic lesion of the distal end of the first metacarpal, but no reactive bone formation. On May 13, 1948, exploration of the sinus revealed a large piece of rose thorn with several smaller fragments in a bed of granulation tissue. The cavity was curetted and drained, and the wound was permitted to heal by secondary intention.

Final examination three months after removal of the thorn revealed full range of motion of the thumb without pain.

Experience with the third case indicates the need for a high degree of suspicion in making the diagnosis of inclusion of organic material near bone.

FIG. 3

Case 3. C. M. Showing "onion peeling" and expansion of the mid-shaft of the fibula.

CASE 3.† C. M., six years old, white, male. This child's presenting complaint was tenderness and swelling on the lateral aspect of the right leg just below the knee. He insisted that he had a splinter in his leg, but this was denied by his parents and thought unlikely by the surgeon, since there was no evidence of a puncture wound. Physical abnormalities were limited to the left lower extremity, where there was tenderness and swelling but no redness over the lateral aspect of the middle third of the leg. Roentgenograms (Fig. 3) revealed the "onion peeling" and expansion of the mid-shaft of the fibula, typical of Ewing's sarcoma.

On July 24, 1936, a biopsy was done and tissue was removed from the center of the lesion. Microscopically this showed granulomatous changes, non-specific in nature; but in one of the sections a date palm thorn was identified. The postoperative course was uneventful, and roentgenograms made three months after the biopsy revealed almost normal contour of the bone.

† Through the courtesy of Harold E. Crowe, M.D., Los Angeles, California.

SUMMARY

Certain plant thorns in or near bone can cause a reaction in this tissue which may simulate a neoplasm or granuloma. The author has been able to uncover three cases. It is not known whether other organic material will cause a similar reaction. It is evident that most organic materials, such as catgut, do not cause such response in bone.

The physician should maintain a high degree of suspicion to rule out the possibility of organic material causing reaction in bone and consider it in the roentgenographic differential diagnosis of bone neoplasia.

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AN ELECTRON-MICROSCOPIC STUDY OF THE CRYSTALLINE INORGANIC COMPONENT OF BONE AND ITS RELATIONSHIP TO THE ORGANIC MATRIX *

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INTRODUCTION

The inorganic and organic parts are combined in living bone so that they form a very efficient frame or skeleton in view of its weight [47,77,123]. Dead bone, in which this relationship degenerates, *gradually* loses its efficient structural characteristics [4].

A large amount of time and effort has been devoted to the problem of bone structure at the microscopic and submicroscopic levels by many investigators. *Bundles* of collagen fibers can be studied with the light microscope [6,101,102,122] and polarized light [105,106,113], while the bone crystals can be *indirectly* studied by x-ray diffraction and polarized-light methods [9,19,25,29,56,58,62,98,113]. Orientation of crystals and collagen fibers in bone and teeth have been suggested on the basis of data from x-ray diffraction [11,25,27,28,107] and polarized light [75,105,106,113,114]. A large literature has grown up about such studies; but, although these methods and their results are exceedingly valuable, they do not actually allow one to see the inorganic bone crystals, or to visualize directly the relation these crystals hold to one another, to the cement substance, and to the scleroprotein fibers. They do not permit direct measurement of the length, width, and thickness of the bone crystals and collagen fibers as does the electron-micrographic method.

Two years ago a method of preparing bone for the electron microscope was found [100]. This simple blending method of preparing fresh bone, and bone from which the organic matter has been removed, is important, for it has been the means of revealing the structural organic and inorganic units of bone by electron micrographs.

The electron micrographs of inorganic bone crystals facilitate the understanding of recent concepts concerning the uniformity of size and singleness of type of the inorganic crystalline component of bone, inorganic atomic exchange in bone, and the spatial relations of the collagen fibers, cement substance, and inorganic crystals. A correlation of the electron micrographs of these structural units with the modern concepts of bone metabolism is made in this paper.

BACKGROUND MATERIAL

A. *Major Components of Bone and the Sequence of Their Development*

Anatomically bone is divided into two major parts: the organic and the inorganic (the water is almost entirely in the organic component). Chemically bone is divided into three parts: (the water component is considered separately).

The organic part can be subdivided into three components:

1. *The cells,*—that is, osteoblasts, osteocytes, and osteoclasts [4,15,122]. These cells contain phospholipids, protein, nucleoprotein, potassium, and some of the magnesium.

2. *The "crystalline" component* or scleroprotein fibers,—that is, collagen [5,25,27,62,102,122]. This component contains amino acids, sulphates, and phosphates. The term "crystalline" is used since collagen fibers give an x-ray diffraction pattern [107]. Just as only part of the inorganic salts are in crystalline form, so only a part of the protein in bone is in a "crystalline" form. The first chemical breakdown product of collagen is gelatin [27,111].

* Read in part at the Annual Meeting of The American Orthopaedic Association, White Sulphur Springs, West Virginia, June 20, 1951.

3. *The cement substance* which is apparently composed of hexoses in a mucopolysaccharide form; and of hexoses in various degrees of combination with protein as glycoprotein [35,71]. A large part of the body magnesium, 90 per cent. of the body citrate [32,33], 80 per cent. of the body carbonate [37], 25 per cent. of the body sodium [53], and some calcium and phosphate excess to the crystals are apparently contained in this component in a non-crystalline, partly diffusible state.

Water comprises about 20 per cent. or more of bone. Part of the water is in the cells and part is in the cement substance and collagen fibers. Only a very small part is in the inorganic crystals [39,120].

The inorganic part of bone can be separated into two components:

1. *The crystalline* which is composed of hydroxyapatite crystals [9]. These have a specific gravity of 3.0 [88] and have the basic formula $Ca_{10}P_6O_{26}H_2$. These atoms are arranged in the atomic lattice characteristic of apatite [8,9,13,113] (Fig. 1-F).

2. *The non-crystalline inorganic component:* Sodium, magnesium, calcium, phosphate, with trace quantities of other inorganic substances are understood to lie in the cement substance about the crystals of hydroxyapatite. It should also be noted that there is apparently a close combination of carbonate with the surface of the inorganic crystalline phase and it has been considered in most inorganic analyses of bone in the past [3,16,55,56,57,59].

Table I is constructed so as to correlate the chemical and anatomical divisions of bone and to show particularly what place the inorganic crystals take in the chemical composition of bone.

Table I takes cognizance of the fact that part of the inorganic material is not in crystalline form. The carbonate has usually been considered in the inorganic part; but since it apparently resides in the cement substance peripheral to the crystals and is lost on ashing, it was placed, along with sulphates and chlorides, in the "organic" section of Table I. Carbonate is very interesting, for it shows how some of the non-crystalline inorganic reservoir may equilibrate with a normal constituent of the crystalline part. In rickets the body phosphate is decreased and the bone phosphate falls while the bone carbonate rises [70]. Conversely, Sobel has been able experimentally to raise the bone phosphate and to lower the bone carbonate [110].

The crystals, despite variations in the total inorganic pattern of bone in the fresh state, remain hydroxyapatite. Therefore, in Table I all crystals are listed as hydroxyapatite.

Potassium occurs in amounts expected in the intracellular fluid [52,53]. Some magnesium may be intracellular.

Water is given a significant place because that portion of water which is not in the cells seems to be largely held in the amorphous cement substance. It seems probable that the water content of bone partly reflects the physical state of the matrix, particularly the cement substance. Water rises as high as 60 per cent. in forming bone, and it drops as low as 10 per cent. in senile cortical bone.

The organic part of bone usually comprises over half its weight and about two thirds of its volume. The largest part of the dry organic component is the protein, part of which occurs in polypeptide chains as collagen fibers. These give an x-ray diffraction pattern and have, therefore, been called the *crystalline* part of the organic matrix. The gelatin nitrogen represents the protein in the collagen fibers [79,111]. The non-gelatin nitrogen represents the protein in the cement substance and cells. The cement substance is now believed to be made up of a whole spectrum of hexose-protein combinations ranging from mucopolysaccharides (that is, polymerized hexoses containing sulphate, and apparently closely related to chondroitin sulphate of cartilage) at one end, to glycoprotein (that is, a hexose-protein in which the protein moiety overshadows the hexose) at the other end.

Grossly flexible bone (such as a sheet of cortex of the distal part of a rib, or cancel-

TABLE I

Components	Partial Divisions	Cancellous						Compact		
		Young Bone			Old Bone					
		Wgt. (*gm.*)	Vol. (*c.c.*)	Spec. Grav.	Wgt. (*gm.*)	Vol. (*c.c.*)	Spec. Grav.	Wgt. (*gm.*)	Vol. (*c.c.*)	Spec. Grav.
Inorganic: References: 1, 8, 9, 13, 19, 61, 62, 63, 76	1. *Crystalline:* Hydroxyapatite crystals	37.5	12.1	3.0	43.7	14.1	3.0	46.5	15	3.0
References: 14, 16, 17, 21, 23, 52, 53, 56, 63, 77	2. *Non-Crystalline:* Inorganic elements external to crystals, in cement substance or cells or collagen fibers. K, Na, Mg, Ca, plus 20 ± trace elements	3.3	1.7	1.9	2.9	1.5	1.7	3.5	1.7	2.0
References: 72, 77, 119, 120, 121	Ash weight of 100 grams of fresh bone	40.8	13.8	2.9	46.6	15.6	2.9	50	16.7	2.9
Organic: References: 7, 79, 111	1. *Crystalline:* Collagen fibers a. Protein (gelatin nitrogen) 50–65 per cent. of total nitrogen	23			25			30		
Reference: 84	2. *Non-Crystalline:* a. Protein (non-gelatin nitrogen) 35–50 per cent. of total nitrogen									
References: 32, 33, 37, 71, 84	b. Fat	6.2			8.4			5		
	c. Other organic components plus anions associated with organic matrix									
	Organic weight	29.2	16.7	1.7	33.4	18.9	1.7	35	20	1.7
Reference: 119	Organic weight + ash weight = dry-bone weight	70	30.5		80	34.5		85	36.7	
Water: References: 22, 39, 52, 120		30	30	1.0	20	20	1.0	15	15	1.0
	Water + organic weight =	59.2	47.2		53.4	38.9		50	35	
Total: References: 72, 119	100 grams of fresh, hydrated bone without marrow	100	60.5	1.6	100	54.5	1.8	100	51.7	1.9
Constant: Reference: 119	$\frac{\text{Ash weight}}{\text{Dry weight}}$ = 58.3 per cent. with a normal range from 54.5 to 62.1 per cent.	$\frac{40.8}{70}$ = 58.3 per cent.			$\frac{46.6}{80}$ = 58.3 per cent.			$\frac{50}{85}$ = 58.8 per cent.		

lous bone, or a long bone from an immature animal) contains more organic and less inorganic material per cubic centimeter than the inflexible cortex of a mature long bone [77]. (When seen in the electron microscope, flexible bone shows a looser packing of inorganic crystals and the crystal-encrusted collagen fibers are more easily seen than in samples of blended cortex of rigid, mature long bone. Examples of this are to be found in Electron Micrographs 1 and 2.)

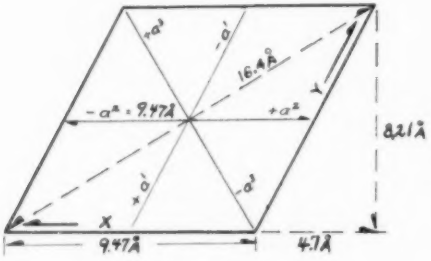


FIG. 1-A

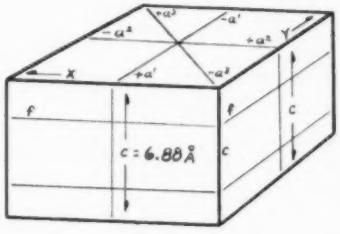


FIG. 1-B

Fig. 1-A: This is the projection of one of the two quadrilateral surfaces of a unit cell. The three *A* axes are illustrated. These are isometric and are at an angle of 60 degrees to one another, lying in a plane which is perpendicular to the *C* axis shown in Fig. 1-B. The three *A* axes are 9.47 Angström units in length [9]. The *XY* coordinates of the unit cell are shown.

Fig. 1-B: This unit cell perspective shows the relation of the rectangular side to the quadrilateral surface illustrated in Fig. 1-A. The *C* axis is 6.88 Angström units in length [9]. The two reflection planes are marked *F*.

Fig. 1-C: This is an enlargement of Fig. 1-B and shows the general arrangement of the Ca, OH, PO_4 groups that make up one unit cell of hydroxyapatite. They are in this figure distributed about two reflection planes (*F*). The atoms composing these groups form a lattice so arranged that each half of the unit cell is a mirror image of the other half (Fig. 1-F). Of course, the space that these atoms actually occupy fills the whole volume of the unit cell [127], but in this diagram they are separated in order to clarify their relative position. *Since the unit cell is an arbitrary division of a continuous lattice of atoms regularly arranged,* each one is continuous on four sides with identical unit cells. Therefore, the contiguous atoms are shared.

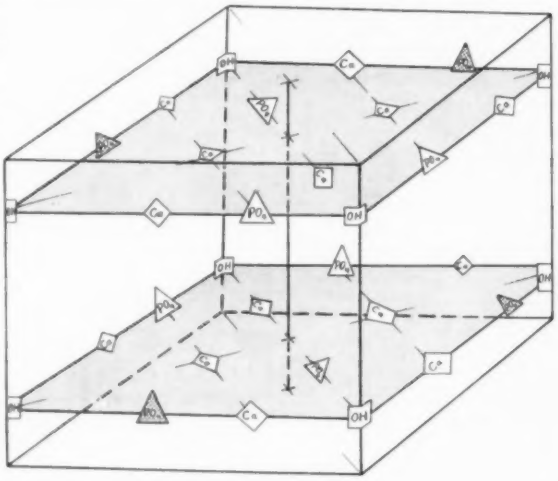


FIG. 1-C

To attempt a correlation of the atomic lattice with the chemical formula $[CaOH{\cdot}Ca_4(PO_4)_3]_2$, the following analysis of the unit cell is made:

Ten calcium atoms: The six (Ca) in the center belong only to this unit cell while the eight (Ca) in the periphery are shared with neighboring units, so that only four of these can be said to belong exclusively to this unit cell.

Six phosphate ions: The two (PO_4) in the center belong only to this unit cell, while the eight (PO_4) in the periphery are shared with four neighboring units, so that only four belong exclusively to this unit cell. Actually, the (PO_4) groups, being relatively large, are eccentrically placed (Fig. 1-F). The cross-hatched groups lie within adjacent unit cells, while the unmarked groups lie within the unit cell diagrammed.

Two hydroxyl ions: The eight (OH) on the four corners of the unit cell are shared by a total of eight unit cells. (This can be seen in Fig. 1-E.) In other words, four unit cells share two (OH) at each corner. Therefore, at each corner any one unit cell can only claim one-half (OH). Each unit cell has four corners, so that there are two (OH) to each unit cell.

By adding the subheadings together, we obtain $Ca_{10}H_2P_6O_{26}$, which contains the same number of atoms as $[CaOH{\cdot}Ca_4(PO_4)_3]_2$. This ratio of atoms maintained in a continuous lattice so that each atom bears a constant recurring spatial relationship to the others is the basis of the crystalline component of bone. The calcium-phosphorus ratio by weight in such an atomic lattice is 2.16.

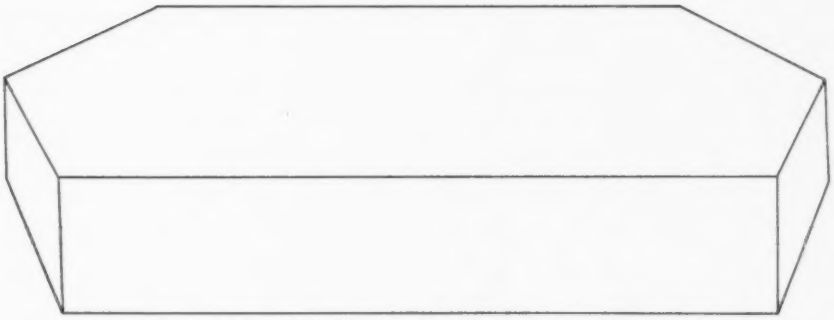


FIG. 1-D

A hydroxyapatite bone crystal (see E.M. 8) drawn in perspective to represent a mature, tabular, hexagonal crystal.

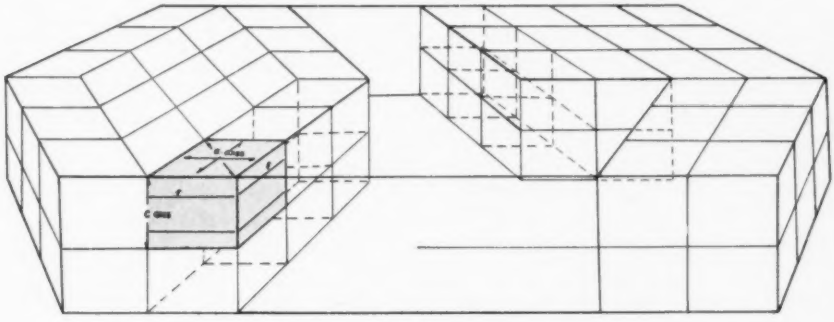


FIG. 1-E

The break-down of the tabular crystal shown in Fig. 1-D into an arbitrary unit-cell division is shown. The ratio of length to width to thickness of these crystals is approximately 10 to 5 to 2. On the periphery of the crystals the atomic lattice pattern is undoubtedly incomplete in many crystals. It is in this peripheral zone that the organic-inorganic interface exists between the cement substance and the crystals. Some evidence suggests that the unit cell may lie with the *C* axis in the long crystal axis [112].

Various analyses of bone have been reviewed (references in Table I) and a generalized approximation of the data is recorded in Table I. It is to be particularly noted that the composition of bone changes with age, the water content decreasing markedly, while the total ash rises [84]. The magnesium decreases as the calcium increases. The phosphorus rises slowly, then falls after forty or fifty years, while the phosphatase varies in inverse relation with the phosphorus [120]. The carbonate and the organic matter (water-free) increases with age; the fat shows changes, and its phospholipid component decreases with age [84]. The organic and water components constitute 70 to 75 per cent. of the volume of bone.

A characteristic cement substance apparently accounts for the calcification of bone. Wolbach [124,125] and Follis [36] have both observed that vitamin C is necessary for the formation of adequate matrix about the osteoblasts and particularly for the formation of collagen fibers in this matrix. Copp [30] has shown that in the experimental animal *some* phosphate is necessary for the formation of matrix. With phosphate intake somewhat above minimal requirements, matrix forms in rachitic animals but is not calcified; with phosphate intake below minimal requirements, a very scanty matrix is formed—not the wide osteoid bands of florid rickets. Therefore, it would seem that both vitamin C and minimal amounts of phosphate are necessary for the formation of an adequate matrix.

Vitamin C is also necessary for the collagen-fiber development which occurs in that matrix.[79]

Baker [5] has noted that calcification does not occur in bone matrix until the collagen fibers have appeared. Henschen [60,61,64] has shown that, by x-ray diffraction of fracture callus, the organic *crystalline* pattern of the collagen appears before the inorganic hydroxyapatite crystalline pattern.

Finally, Follis [35] has noted a more intense staining of the cement substance with metachromatic dyes in the general region of developing collagen fibers in a calcifying skeletal matrix. It is in the cement substance *about the fibers* that the hydroxyapatite crystals first appear [105]. (It is in these regions of fiber-crystal approximation that electron micrographs show co-orientation such as that seen in Electron Micrographs 21, 24, and 26.)

Maturing of the bone matrix, shown by the formation of collagen fibers, and chemical changes in the cement substance, denoted by special staining reactions about the fibers, seem necessary precursors to the appearance of the inorganic hydroxyapatite crystals in the bone matrix.

The collagen fibers of the matrix of bone appear about the same in the electron microscope as do the fibers of tendon, hyaline cartilage, or fibrocartilage.[48] Chemically there may be a difference in the reacting side chain of the polypeptide units forming the collagen fibers in various fibrous tissues. As yet, however, no specific differences in collagen have been noted in these electron micrographs, or in the more complete studies by other investigators that have come to our attention [38,40,107]. Viewed through the electron microscope, collagen seems to be similar wherever it occurs.

However, *the cement substance* of bone matrix is probably *different* from that of other connective tissues. This difference is not directly apparent in the electron microscope at present. However, histologists using special histochemical techniques have noted a staining specificity of calcifying cement substance; in fact, they suggest that, when a matrix stains in a certain way with metachromatic dyes, one may suppose that that matrix is destined to become calcified [35,79]. By chemical analysis the cement substance of bone apparently contains mucopolysaccharides slightly different from those isolated from the cement substance of connective tissues which do not usually calcify [71].

The cell morphology in newly forming bone may not be definite enough to differentiate it from others of the reticulum-cell series [15]. However, the matrix which such an osteoblast produces and controls is apparently characteristic and, under normal conditions, sets apart that variant of the reticulum-cell series which produces it [125]. Evidence suggests that the cement substance of this matrix has a variable ability to detain calcium from, or to release it into, adjoining extracellular fluid [17]. Unlike the matrix of costocartilage, which will transmit radio-active calcium quickly to or from a small group of hydroxyapatite crystals buried in it [99] but which will not precipitate such calcium as crystals, the matrix of bone will under normal conditions pick up calcium quickly and deposit it in the cement substance (about as fast as the matrix matures) as hydroxyapatite crystals [115,116,117]. However, this mechanism is altered in low-phosphorus rickets [30]. The crystallization mechanism depends on a variety of factors, such as adequate circulating phosphate, the development of collagen fibers, and a normal carbohydrate and protein metabolism of the osteocytes [24]. However, these latter factors being within normal limits, the typical calcification of bone matrix seems to depend on some special properties of the mucopolysaccharide-glycoprotein complex (the cement substance) of the bone matrix.

Discussing the general problem of calcification of cartilage at the epiphyseal line, Gutman [59] said, "I have no information on how the actual deposition of bone salt in the matrix occurs. Presumably the actual precipitation of bone salt is determined by the solubility product of some calcium salt. However, it is possible that the protein-polysaccharide matrix forms a complex salt with calcium and phosphate, and molecular rearrange-

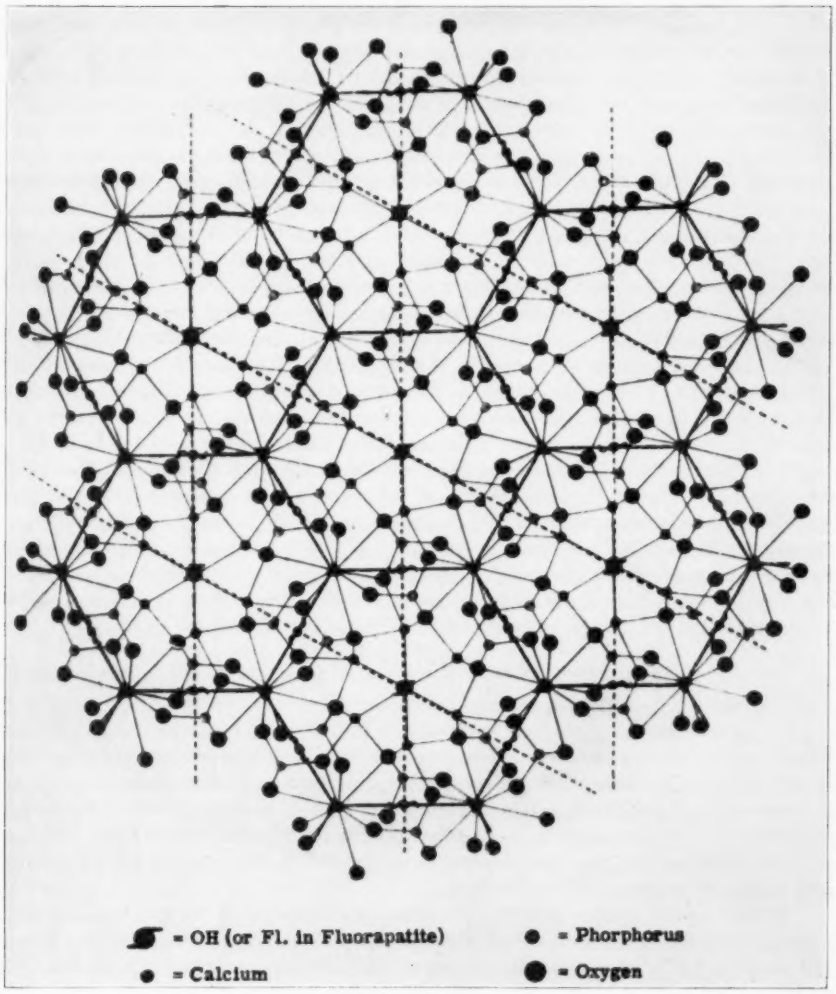


FIG. 1-F

The atomic lattice of apatite

From "The Atomic Structure of Fluorapatite and Its Relations to That of Tooth and Bone Material", Fig. 5. (Used by the courtesy of the authors, C. A. Beevers and D. B. McIntyre, and with the permission of the *Mineralogical Magazine*.)[12]

ments effect formation of bone salts in a manner which does not involve precipitation in the ordinary sense; hence studies of solubility products may be irrelevant to the problem of calcification in cartilage. Such studies, on the other hand, may be critical for the deposition of calcium salts associated with hyperphosphatemia due to renal insufficiency and secondary hyperparathyroidism."

On the basis of experimental and clinical observations, it seems fair to summarize a present-day concept of bone formation, metabolism, and breakdown in this way: Bone is formed by cells which are special derivatives of the mesenchyme and, in the adult organism, from the reticulum cell. The cells, when anabolizing bone, are called osteoblasts; when metabolizing bone, they are called osteocytes; and when catabolizing bone, they are

called osteoclasts [15,54,85,86,87]. In the presence of an adequate stimulus, adequate organic building blocks, and with adequate essential inorganic material (such as phosphorus), *the osteoblast produces a primitive matrix.* This matrix is composed of a mixture of hexoses and amino acids with a high sulphate and water content. Phosphatase makes its appearance about this time in the cell, and probably a little later in the matrix. The question of whether phosphatase is primarily associated with matrix maturation or with crystal formation, or both, in bone cannot be answered at present. High-energy phosphate seems essential for the formation of the peptide bond [90,96]. During the process of matrix maturation collagen fibers appear in it. *The matrix, when mature, is composed of scleroprotein fibers, called collagen fibers, and cement substance.* When the matrix is mature,—that is, when it contains collagen fibers—and when the cement substance stains metachromatically, then and only then does the cement substance become filled with the hydroxyapatite crystals, which make bone hard, give it strength to act as a skeletal tissue, and, finally, make it radiopaque. Of course, in normally developing bone these processes follow one another in rapid succession so that it is hard to divide one stage of development from another; but in diseases the development may be halted at various stages and thus the steps of the process have been partly revealed. For instance, scurvy not only limits the ability of the osteoblast to produce matrix, but it will also stop the collagen-fiber formation in primitive matrix [79] and calcified bone is not formed. In rickets, on the other hand, the cells can produce the matrix with collagen fibers; but the inorganic calcium and phosphorus are not available to the matrix and calcified bone is not formed. It is quite possible that someone may one day be able to describe a metabolic disease of bone in which the primitive matrix is formed abundantly but in which collagen fibers do not appear; the matrix would not mature properly and calcified bone would not be formed.

B. *Knowledge of Bone Crystals Gained by Methods of Investigation Other than the Electron Microscope*

1. *The arrangement of atoms in the inorganic bone crystals:* It has been shown by x-ray diffraction studies that the inorganic component of bone is largely crystalline and is not amorphous [63,76]. The crystalline phase of the inorganic component of bone is known to be hydroxyapatite and not some other calcium-phosphate crystal [9,19,20]. The patterns in Figure 3 were made from bone samples used in the electron microscope; they were made to check on the electron-microscope findings to be sure that one was observing hydroxyapatite crystals and not artifacts.

On the basis of similar patterns, physicists have calculated the arrangement of the calcium, phosphorus, oxygen, and hydrogen atoms in relation to one another in bone crystals (Fig. 1-F). They have determined the size and shape of one homogenous part, or *unit cell,* of such an atomic lattice [9,13,93,127]; and they have calculated the approximate size of the crystals [19]. The calculated specific gravity of hydroxyapatite is 3.0 [88,92] and the calculated calcium to phosphorus ratio is 2.16. On the basis of such work, Figures 1-A, 1-B, and 1-C were drawn. They show the shape and the space occupied by an arbitrary division of the atomic lattice of hydroxyapatite, a unit cell,—the smallest homogenous combination of Ca, PO_4 and OH groups which possess the characteristics of hydroxyapatite. The crystals are a continuum of such arbitrary divisions of the atomic lattice. The larger the crystal, the more extensive are the atomic reflection planes (two of which are shown in Fig. 1-C, shaded), and the better is the pattern made by the monocromatic x-ray beam that is reflected by these planes. The pattern made by bone crystals is characterized by somewhat fuzzy and rather broad lines. From this fact it was concluded that the bone crystals were very small, between 10,000 and 10 Angström units in length (Table VI).

In normal bone, large crystals never occur [9] (Table VI). The size limitation of the crystals in bone has been an impediment to easy definition of the characteristic atomic

spacing of the unit cell of bone crystals. This probably accounts for the many reported small differences in the unit-cell dimensions of the bone crystals [9, 19, 25, 49, 55, 59, 88, 93, 98, 113].

On the basis of x-ray diffraction studies, the idea was conceived that bone crystals, although very tiny, should be large enough to be viewed in the electron microscope which has an optimal resolving power of 20 Angström units. Although the crystals might be seen by electron micrography, the unit cells could not be visualized, for in one sense any bimolecular subdivision of an atomic crystal lattice is arbitrary. Each crystal seen in the electron microscope can be only arbitrarily subdivided into several thousand unit cells (Figs. 1-E and 1-F). The hydroxyapatite crystals may vary in size, but the atom groups of which they are composed are identical (Table VI).

The chemical composition of the bone, enamel, and dentine crystals [3] has been the subject of a great deal of discussion. The arguments, however, have been resolved to this: Chemically, the unit cells of the crystals have been called a double molecule of hydroxyapatite with the formula $[Ca(OH)\cdot Ca_4(PO_4)_3]_2$. To comprehend this resolution of past arguments, several major points in the modern understanding of inorganic bone crystals must be considered.

First, the bone crystals can *adsorb* a great number of ions (for example, carbonate, citrate, sodium, magnesium, and phosphate ions) to their periphery [56]. They also *adsorb* gases [56, 126].

Second, the bone crystals exchange certain *compatible adsorbed* atoms for those already in their lattice; at least into the periphery of the lattice. These can consist of iso-ionic exchanges, as when calcium exchanges for a calcium, a phosphate for a phosphate, or a hydroxyl for a hydroxyl ion. They may occasionally consist of hetero-ionic exchanges, such as fluorine for the hydroxyl group [94].

However, even in bone from rabbits with fluorine poisoning, the atomic pattern is that of hydroxyapatite. The supposition is that the fluorine, in sublethal concentration at least, can only occupy peripheral (OH) positions on the crystals or it is mostly present in the matrix [56, 74, 98]. Only a very small number (5 to 10 per cent.) of the unit cells could show fluorine substitution in the lattice before showing up on x-ray diffraction of bone, with the equipment used by Brandenburger and Schinz; and yet, no such pattern could be seen in fresh bone from rabbits with fluorine poisoning by these investigators.

Third, iso-ionic *migration* of calcium, phosphorus, and hydroxyl ions into the depths of a bone crystal may occur [95]. Perhaps, hetero-ionic *migration* of ions, such as fluoride, is also possible; but, as noted above, there is some doubt that this may occur in living bone even in cases of fluorine poisoning [19].

Environment, diet, and variations in general health can change the inorganic composition of the extracellular fluids and the cement substance of bone, but bone crystals remain hydroxyapatite. For purposes of naming the inorganic crystal constituent of bone, variations in the total inorganic composition of bone are not important. The problem is resolved by naming the atomic-lattice pattern that predominates (at least 95 per cent.) in the x-ray diffraction pattern of fresh, deproteinized, and heat-ashed bone. That constant inorganic crystal constituent is hydroxyapatite. It is the only pattern found in the inorganic part of fresh normal and abnormal bone, enamel, dentine, and most soft-tissue calcifications [9, 19] (Tables IV and V). Abnormal calcifications (*not bone*) may give other patterns [19], but they usually give that of hydroxyapatite.

As more attention is being focused on tissue depots in physiological chemistry, bone is becoming recognized as a base for calcium, phosphorus, magnesium, sodium, carbonate, and citrate. With this in mind, Brandenburger and Schinz stated that, without the appearance of any other crystal type than that of hydroxyapatite, the composition of the inorganic component of bone may diverge considerably from the ideal composition of hydroxyapatite. It is entirely impossible to draw a conclusion as to the existence of certain crystal types in the inorganic bone substance by the exclusive use of analytical chemical

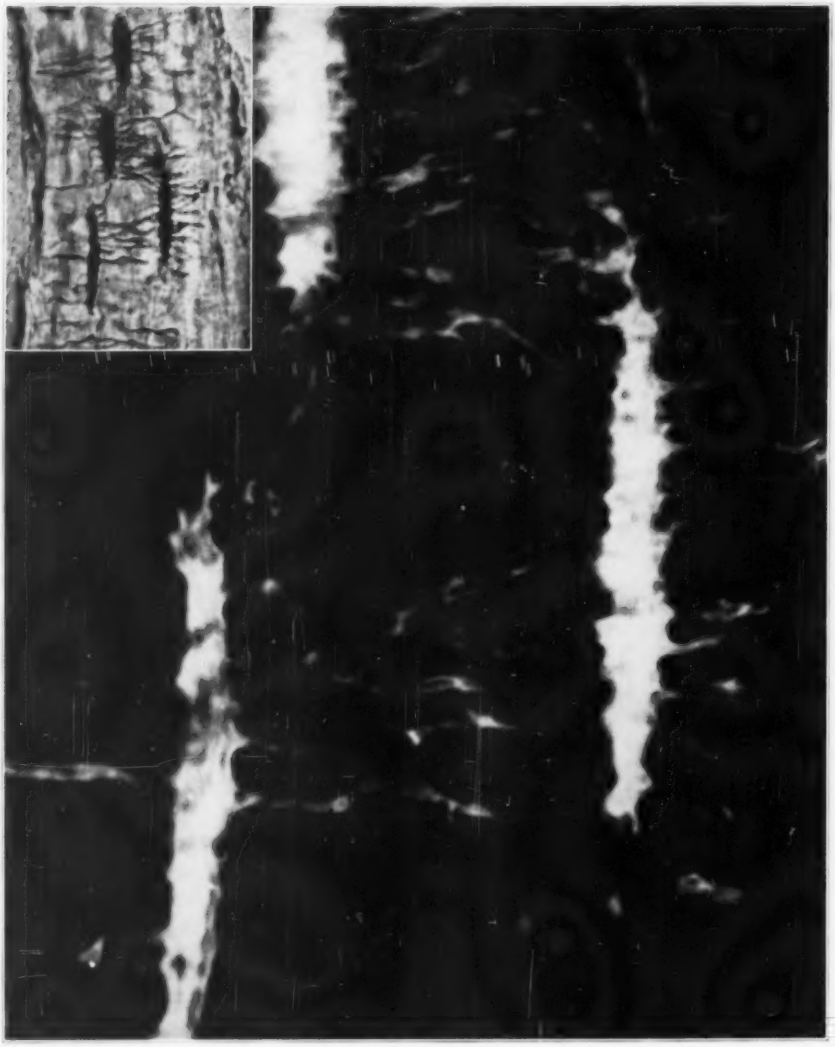


FIG. 2-A and FIG. 2-B

Fig. 2-A: In the upper corner one sees a micrograph of a fragment of autoclaved bone (magnification 500 ×). The many canaliculi should be noted for in the living bone the protoplasmic syncytium of the osteocytes passes through these. This protoplasmic syncytium extends from the areas of extracellular fluid near the nutrient blood supply to the depth of the trabeculae or to the periphery of a Haversian unit. The matrix and its metabolic control is believed to emanate from this syncytium.

Fig. 2-B: Fig. 2-A, greatly enlarged (magnification 7,000 ×).

data. The same holds true of ectopic calcifications. The chemical composition of such calcium depots does not necessarily need to correspond to the composition of the crystals present therein; but it can be determined only as an overlay of the chemical composition of inorganic crystals and of amorphous inorganic particles of bone or aberrant calcifications as, for instance, the adsorption sheath around the crystals.

A chemical approach to the formation of hydroxyapatite crystals may be found in

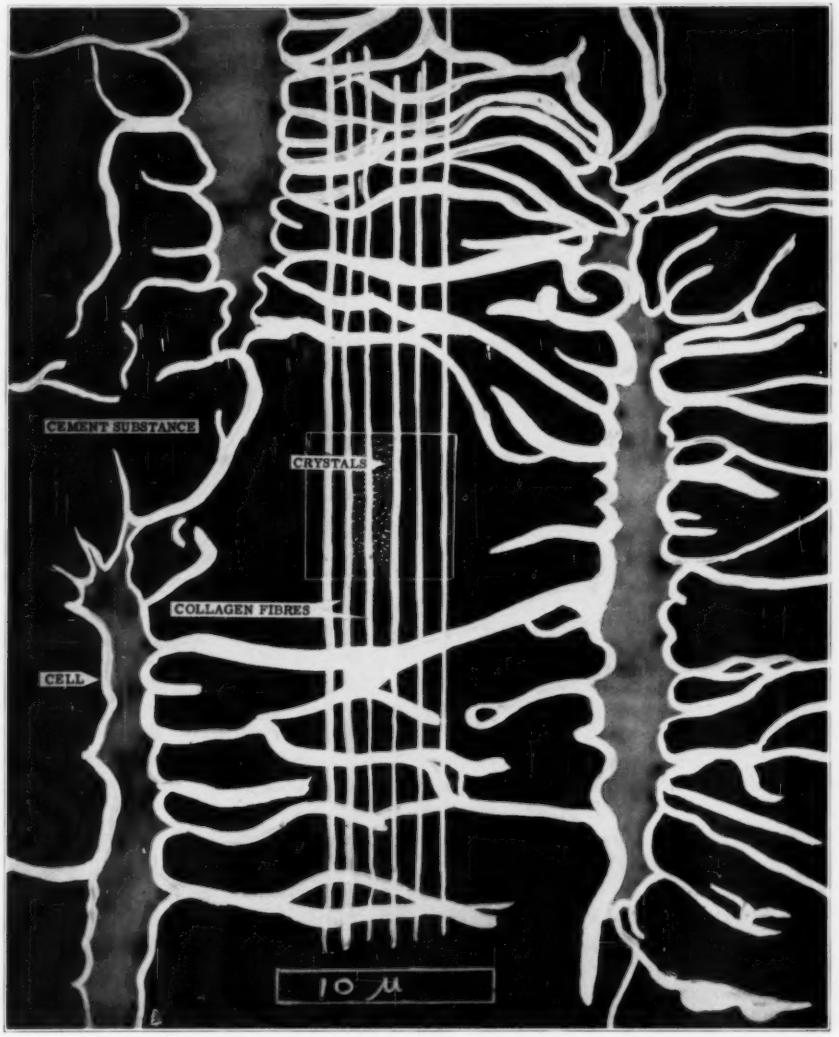


FIG. 2-C

Same as Fig. 2-B, with tracing of the lacunar and canalicular outlines. Perpendicular lines representing collagen fibers have been diagrammatically sketched into the background. This does not imply that the collagen fibers normally lie in this linear relationship to the osteocyte. The central square shows the relative size of the field of the electron microscope when set for magnification of objects at about 7,000 ×. The small dots in the box represent the bone crystals. Obviously, the osteocyte is too big to be observed in one field of the electron microscope at this enlargement but the crystals, the collagen fibers, and the cement substance (which is represented by the black background) should be visible in one such field. The purpose of Figs. 2-A through 2-C is to orient the reader by reference to light micrographs to the range of the electron microscope.

the experiments of Larson, Moeller and von Troemel, Hodge, Le Fevre, and Bale, and Hodge [67]. They studied crystals precipitated from controlled combinations of calcium and phosphate solutions. One conclusion to be drawn from these experiments is nicely

TABLE II

TABLE OF MEASURES FOR ILLUSTRATIONS

The wave length of visible light is 4,000 Angström units to 8,000 Angström units or 0.4 to 0.8 micron.
The maximum resolution of the light microscope is about 2,000 Angström units.
The maximum resolution of the R.C.A. "E.M.U." electron microscope is about 20 Angström units.

	1,000 micra =	1 mm. =	1/10 cm. = 10^{-1} cm.	
	100 micra =	1/10 mm. =	1/100 cm. = 10^{-2} cm.	
	10 micra =	1/100 mm. =	1/1,000 cm. = 10^{-3} cm.	
1 μ	1 micron =	1/1,000 mm. =	1/10,000 cm. = 10^{-4} cm. =	10,000 Å.
	1/10 micron =	1/10,000 mm. =	1/100,000 cm. = 10^{-5} cm. =	1,000 Å.
	1/100 micron =	1/100,000 mm. =	1/1,000,000 cm. = 10^{-6} cm. =	100 Å.
1 mμ	1/1,000 micron =	1/1,000,000 mm. =	1/10,000,000 cm. = 10^{-7} cm. =	10 Å.
	1/10,000 micron =	1/10,000,000 mm. =	1/100,000,000 cm. = 10^{-8} cm. =	1 Å.
	1/100,000 micron =	1/100,000,000 mm. =	1/1,000,000,000 cm. = 10^{-9} cm. =	0.1 Å.
1 $\mu\mu$	1/1,000,000 micron =	1/1,000,000,000 mm. =	1/10,000,000,000 cm. = 10^{-10} cm. =	0.01 Å.

Unit of Measure for Enlargements

At magnification of 26,000, one millimeter will equal 385 Angström units (Å).
At magnification of 30,000, one millimeter will equal 330 Angström units (Å).
At magnification of 34,500, one millimeter will equal 290 Angström units (Å).
At magnification of 42,000, one millimeter will equal 240 Angström units (Å).
At magnification of 64,000, one millimeter will equal 160 Angström units (Å).

summarized by Brandenburger and Schinz and is important when one speculates about the fact that most normal and abnormal soft-tissue calcifications in man are hydroxyapatite and not some other calcium-phosphate crystal: Calcium-phosphate precipitation over a very wide range of concentration consists almost exclusively of hydroxyapatite and this compound constitutes the predominant crystal type in the system CaO-P_2O_5-H_2O, at least in the wide range of possible hydroxyapatite existence or development. . . . The sharp preferential selection which we found in calcifications in the human organism to the crystal type of apatite as the major inorganic component not only of bone, both in health and disease, but of aberrant bone and pathological calcifications, is nothing else but the expression of the peculiarity inherent in the inorganic system CaO-P_2O_5-H_2O. It is not an effect of the presence of this system in the human organism.

Even the most abnormal calcifications in man have hydroxyapatite as their crystalline component but in certain abnormal calcifications in man (Table IV) there is probably an excess of phosphate ion adsorbed to the hydroxyapatite crystal. This excess was marked in the tartar from human teeth, prostatic calculus, salivary calculus, from affected bone in Hodgkin's disease, and not so marked in two of four calcified rib cartilages, a venous calculus, and specimens from subjects with calcinosis universalis studied by Brandenburger and Schinz. The excess adsorbed phosphate only showed up in the crystal lattice after heating the specimen above 400 degrees centigrade.

2. *Crystal shape:* Brandenburger and Schinz mention the theoretically possible shapes of bone crystals and point out that the habit of hydroxyapatite crystals might be isometric *hexagons*, but they could also occur as *tabular* forms, and *needles, especially when the crystal sizes are small.* The electron micrographs show the crystals of bone to be tabular in habit. Crystals from a supraspinatus-tendon calcification show both tabular and needle-shaped habits. The enamel crystals appear "ribbon-like". They are probably long, flattened hexagonal prisms [18].

3. *Crystal size:* The sizes of the inorganic bone crystals calculated from x-ray diffraction studies vary. Henschen [63] states that in bone the mineral phase exists as crystals of 2×10^{-8} centimeter to 2×10^{-6} centimeter in length (see Table II). R. Stuehler gave 10^{-7} centimeter. Neuman and Hodge [66], by chemical and physical methods, assuming the

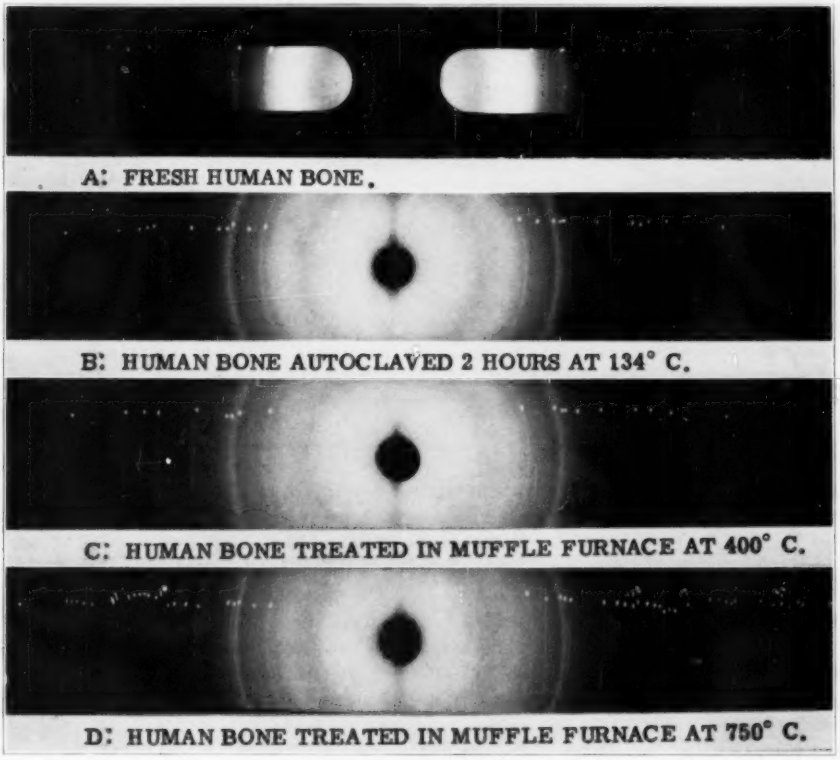

A: FRESH HUMAN BONE.
B: HUMAN BONE AUTOCLAVED 2 HOURS AT 134° C.
C: HUMAN BONE TREATED IN MUFFLE FURNACE AT 400° C.
D: HUMAN BONE TREATED IN MUFFLE FURNACE AT 750° C.

FIG. 3

X-ray diffraction patterns of bone

This series of x-ray diffraction patterns shows the relative clearing of the background as the temperature of the preparation process increases to 400 degrees centigrade, during which process the organic material is removed. The width of the lines which is *inversely* proportional to the area of the atomic reflection planes of the crystals is not narrowed until bone-preparation methods using heat above 400 degrees centigrade are applied. At heat above 400 degrees centigrade the crystals combine to form larger crystals. E. M. 21 is a picture of the material used for x-ray diffraction *A;* E. M. 3, for x-ray diffraction *B;* E. M. 4, for *D.*

crystals to be cubes and the specific gravity as 2, calculated the dimension as 3×10^{-6} centimeter on a side. Brandenburger and Schinz suggested 10^{-6} centimeter as the limits of bone crystal length (that is, 100 Angström units). It is to be pointed out that all these estimates of crystal sizes were obtained by indirect means. The x-ray diffraction lines by which the size of bone crystals has usually been estimated may be broadened by overlying organic lines which complicates determinations of the size of bone crystal, particularly in fresh samples [113].

Concerning abnormal calcifications showing large hydroxyapatite crystals, Brandenburger and Schinz remark that those calcifications which show strikingly good development of apatite crystals demand special interest.

First, the x-ray diffraction pattern can definitely designate the crystal type of apatite as hydroxyapatite and not fluorapatite or carbonate apatite.[19]

Second, the crystals of hydroxyapatite, when formed in bone, usually occur in small size with some imperfections or incompleteness of the lattice pattern. However, in the case of certain calcifications (particularly the crystals from a tuberculous apical focus

TABLE III

Calcite $CaCO_3$ (Hexagonal habit)	Aragonite $CaCO_3$ (Rhombic habit)
Human: Pancreas calculi, 4	(None found in human)
Outer layer of gallstone, 1	
Otoliths of human ear, 1	
Shell of crayfish	Calcium sacs and otoliths of frog
Shell of lobster	Shell of helix pomatia
Otoliths of lobster	Shell of liebespfeil
Otoliths of chicken	Otoliths of pike
Shell of terebratula	
Cover and eggshell of helix pomatia	
Tartar from teeth of a horse	
Crystal length:	*Crystal length:*
a. 100,900 — 10,000 Angström units for human and chicken otoliths	Up to 1,000,000 Angström units
b. Pancreatic calculus crystals up to 1,000,000 Angström units long	
c. Armor shell of lobster and crayfish up to 1,000 Angström units long	

and tooth enamel), they appear large and well developed, as one only sees after heating bone for one hour at 900 degrees centigrade to improve the crystal quality [19] (Fig. 3,*D* and E. M. 4). The different developmental conditions in the different sites of calcification must here be decisive, given by the type of environment in which the crystallization takes place and the composition of the solution from which it is formed. The speed of original crystallization and the possibility that over a long period of time under certain conditions extensive re-crystallization may occur probably both play a part in the formation of the microcrystalline (10^{-2} to 10^{-4} centimeter, as in teeth), as contrasted to the cryptocrystalline (10^{-4} to 10^{-7} centimeter, as in bone and dentine) size of the hydroxyapatite crystals.[19] (Table VI.)

Hendricks, at the Third Metabolic Interrelations Conference, gave a discussion of the bone crystals from a crystallographer's viewpoint [58]. He conceived the growth of the crystals beginning as hydroxyapatite and continuing to grow as hydroxyapatite. If left alone in a pure system with no adventitious material to reach it, the crystal would apparently grow to a much larger size than it actually does in bone. Instead, as it grows in bone, the ions that are excluded from the crystal lattice (that is, carbonate, citrate, sodium, magnesium hydroxide, fluorine, and uranyl, if present), stay on the surface of the crystal. At least, it is suggested that they completely cover the growing crystal and prevent its further growth.

At that point the crystal can start a new surface by covering up the old one and continue to grow with trapped pockets of carbonate in the resulting extension of the crystal. Hendricks believes that this is what happens in the case of enamel where internal crystal clefts seem to hold the carbonate.

At that same point where the original crystal is limited in its growth by the material on its surface, a new crystal can begin, independently, a little removed in space from the first crystal. Hendricks proposes that this situation obtains in bone. From the electron micrographs it is obvious that the crystals in bone are small and that no exception to the general size range (1,200 to ±20 Angström units) of these crystals seems to occur. The hydroxyapatite crystals produced in the test tube and in certain abnormal sites of calcification and in the tooth enamel often grow larger than those seen in bone. It should also be noted that it was found by electron micrography that *the shape as well as the size of the crystals may be different when developed in non-bone matrices.*

There are probably factors not yet clearly defined which limit the size and shape of hydroxyapatite crystals as they develop in various matrices. In the case of bone, one must

TABLE IV *

HYDROXYAPATITE—$Ca_{10}(PO_4)_6(OH)_2$—POSSIBLE HABITS OF CRYSTALS:

1. Hexagonal
2. Tabular
3. Needle-shaped

Those without Excess Adsorbed Phosphate, Giving Hydroxyapatite on Ignition	Some Excess Phosphate Giving beta-$Ca_3P_2O_8$ on Ignition	Those with Much Excess Phosphate Adsorbed, Giving More beta-$Ca_3P_2O_8$ on Ignition
MAN:		
Calcified rib cartilage, 1	Calcified rib cartilages, 2	Tartar
Calculus from a tuberculous apical calcification	Venous calculus specimen from calcinosis universalis	Prostatic calculus
Bone		Bone from patient with Hodgkin's disease
Tooth		
Brain sand		
Chronic bursitis calcium deposit		
Calcification of calcinosis universalis		
Kidney stones, 2		
Calcified aorta		
Prostatic calculi, 3		
Calcified parts of silicotic lung		
Broncholith		
Calcified placenta		
Osteogenic sarcoma		
ANIMALS:		
Shark tooth and vertebra		
Vertebra of cucaria		
Shell of lingula		
Tooth of a horse (especially the enamel)		

* All specimens listed in Table III gave the pattern of hydroxyapatite prior to "ignition" (that is: heating at 700–900 degrees centigrade for one hour).[19]

suppose that the particular relations of mucopolysaccharides, glycoprotein, fat, citric acid, water, carbonate, sodium, magnesium, and collagen fibers in the specific matrix produced by an osteocyte combine in a physical or chemical way to limit the size of the crystals. This may occur in some such manner as has been suggested by Hendricks and Hill.[58]

Bale [9] points out that even in enamel, where the crystals are much larger than in bone, "There has never been any evidence of grain in the diffraction pattern due to crystals of appreciable size in the enamel". No irregularly large crystals were thought to appear in bone or teeth as exceptions to the size range in which they normally occurred.

Moeller and von Troemel give 10^{-5} to 10^{-6} centimeter as the length of the dentine particle, and 10^{-4} centimeter as the length of the enamel particle. It is agreed that the enamel crystals are larger than the bone crystals.[12, 99]

4. *Polarized light:* Polarized light has been used to study the inorganic crystals in teeth and bone. A review of these methods was given by P. C. Kitchen [75] and referred to in detail by Stuehler [113]. A major difference between the methods using polarized light and those using monochromatic x-ray diffraction is that the beam of polarized light is affected by a group of crystals (possibly by only one crystal if it is 2,000 to 4,000 Angström units in length), whereas the x-ray beam is affected by the atomic reflection planes of a crystal. Polarized-light methods are probably somewhat *gross* for knowledge concerning a *single* bone crystal and x-ray diffraction methods are rather *fine*. But electron-

TABLE V

THE FOLLOWING SAMPLES GAVE THE FOLLOWING X-RAY DIFFRACTION PATTERNS PRIOR TO "IGNITION"

1. Beta-calcium phosphate (tertiary form):

   Assumption is made by Brandenburger and Schinz that water solution was not present for this formation since, they point out, a hydroxyapatite lattice is formed in a water solution even in the presence of excess phosphate.
   Calcified tuberculous lung, 1
   Renal stones, 1 of 12

2. Tetra calcium phosphate:

   CaO lines were seen in one *ignited specimen of calcified rib cartilage in addition to well marked apatite lines.* This could be caused by the following reactions during heating:

   a. $CaCO_3 \xrightarrow{\text{heat}} [CaO] + CO_2$

   b. $(4\ CaO.P_2O_5)_3 \xrightarrow[(+\ H_2O)\ \text{at}\ 1{,}050\ \text{degrees}]{\text{heat}} Ca_{12}P_6O_{27}.H_2O \longrightarrow Ca_{10}(PO_4)_6(OH)_2 + (2\ CaO)$

   (Hydroxyapatite)

Calcium carbonate and tetra calcium phosphate crystals may occur in some calcifications in small quantity.[19]

microscopic methods seem directly applicable for dimension determinations when dealing with objects the size of bone crystals (Table II).

5. *X-ray microscope:* At present, the x-ray microscope has not been developed to the point where sufficient magnification or resolution can be obtained to delineate bone crystals. Eventually, as its resolution is increased, this instrument may become a useful tool in bone research. Some investigators have calculated that the optimal resolution theoretically possible with such a microscope as it is now conceived is about 500 Angström units. Such theoretical resolution, if possible, would not be quite adequate for the delineation of many bone crystals.

6. *Stability of the inorganic crystals of bone in relation to bone-preparation methods:* The inorganic component is quite resistant to certain physical changes. In the sample-preparation methods, heat was used in the case of autoclaved bone and glycol-ashed bone. The question has been raised as to how much this treatment changes the appearance of the inorganic crystals.

When the calcium-phosphorus ratio of the fresh sample is about 1.97 to 2.2, hydroxyapatite is heat stable to about 1,400 degrees centigrade. The constancy of the x-ray diffraction pattern before and after heating at 700 to 900 degrees centigrade for one hour is a commonly used test for the homogeneity of hydroxyapatite [10,68] and is used in x-ray diffraction studies on bone [9,19,113] (Tables IV and V).

The bone crystals have a very small content of water of crystallization. A little water may be lost from apatite crystals in dry heat at 100 degrees centigrade. It is conceivable that such water is adsorbed to the crystal surface. The hydration layer about the crystal seems to be so tightly bound, perhaps to the phosphate atoms, that successive amounts are only removed by heating for long periods at 300 degrees centigrade, then 500 degrees centigrade, 750 degrees centigrade, et cetera [78]. Brandenburger and Schinz believe that the columns of oxygen atoms (OH) in the atomic structure of the crystals may be the basis for this heat stability. The heat resistance may be related to the observation that the inorganic bone crystals do not tend to visibly change when subjected to an intense beam of the electron microscope for at least fifteen minutes.

The x-ray diffraction pattern of fresh untreated bone shows a hydroxyapatite pattern but the definition of the lines is poor (Fig. 3, *A*). There is more *clarity* but no *narrowing* of observable x-ray diffraction lines after glycol-ashing at 143 degrees centigrade and auto-

TABLE VI

	Type of Calcification	For Comparison
Microcrystalline (larger sized)	Calculus from a tuberculous apical focus *	Almost the same as ignited ** apatite crystals or ignited bone apatite
Crystals 10^{-3} to 10^{-4} centimeter in length	Enamel of teeth	
	Lymphnode, calcified lens, calcified aorta, venous calculus, tartar, salivary calculus, renal calculus, prostatic calculus (partial)	As in cold-water precipitated hydroxyapatite
Cryptocrystalline (smaller sized)	Calculus from chronic bursitis, brain sand, calcium gout, prostate calculi (partial), calcified rib cartilage, calcified placenta, osteogenic sarcoma	Normal bone apatite
Crystals 10^{-4} to 10^{-7} centimeter in length		As in hot-water precipitated hydroxyapatite

* Brandenburger and Schinz point out: Apatite calcifications as against $CaCO_3$ consist of smaller crystals, imperfect quality, usually less than 1,000 Angström units long. However, in the calculus from the tuberculous apical focus, the crystals may be up to 10,000 Angström units (10^{-4} centimeter) long. At the same time, these larger apatite crystals appear to be built less faultily than the hundred or thousand times smaller ones which occur in the majority of the calcifications.

** "Ignited" = 900 degrees centigrade for one hour.

claving of bone at 132 degrees centigrade (Fig. 3, *B*). It should be noted that the diffraction lines of fresh bone and of bone heated even to 400 degrees centigrade are essentially the same in width (Fig. 3, *C*). This is attributed to the fact that the crystal size does not change when only 400 degrees centigrade heat is used. Clarity is improved at these temperatures by removal of organic matter. Not only is there x-ray evidence that no discernible change occurs in the crystal *size* with autoclaving and glycol-ashing, but also there is the evidence given by the electron microscope to this effect.

At the periphery of the crystals small imperfections in the atomic-lattice pattern probably occur [9]. These peripheral areas may be filled in or changed while bone undergoes autoclaving or glycol-ashing even though the temperatures involved are comparatively low. Neuman states that the crystal surfaces are richer in calcium after such treatment [94]. There might be some slight sharpening of the peripheral outlines of the crystals as observed in the electron microscope due to such a process of crystal-lattice completion, even though the size and shape of the crystals were not altered. The crystals are unquestionably sharper in outline and easier to bring into focus in the electron microscope after these treatments, but most of this increased clarity is considered to be due to the decrease of the organic matrix after autoclaving and glycol-ashing and to better crystal dispersion.

Heating at from 700 to 900 degrees centigrade causes marked *narrowing* of the diffraction lines in the x-ray diffraction pattern of bone (Fig. 3, *D*), and this has been attributed not only to the loss of organic matter but also to the increased size of the crystalline material by the fusion of many small crystals. This explanation of the increased clarity of x-ray diffraction pattern due to the increased size of the bone crystals is borne out by Electron Micrographs 4 and 20.

Although *the size of the crystals may not change* with autoclaving and glycol-ashing as with heating over 400 degrees centigrade, *some other quality of the bone samples* is changed when they are subjected to methods involving temperatures *under* 400 degrees centigrade which remove the organic matrix. Neuman found that "glycol-ashed" bone [31] had an altered ability to exchange phosphate as measured by studies on the exchange of radio-

TABLE VII

Sample	Analyses (*Number*)	Nitrogen (*Milligrams per Gram of Dried Bone*)	Percentage Protein (*Using Factor 6.25*)	Exchangeable Phosphate: Percentage Equilibrated for Ninety-six Hours at 37 degrees Centigrade. Radio-Active PO_4 Buffer 1	Buffer 2	Illustration
Fresh epiphyseal veal bone, blended:						
pre-autoclaving	10	57.2	35.56	*		E.M. 22
postautoclaving	3	16.29	10.18			
Fresh bone, ground, defatted	1 (200 mesh)	49.3	31	26.8	32.1	
	2		32			
Fresh bone, blended, not defatted	1 (200 mesh)	43.2	27	30.2	27.7	E.M. 2
	2	44.9	28			
	3 (resonated)		24			
Supernatant fluid from bone blended in distilled water	1	9.8	6			
	2	8	5			
Fresh bone, ground, defatted, hyaluronidase added			30	25.7	25	E.M. 24
Bone autoclaved at twenty-seven pounds for two hours, blended	1	12.5	7.8	14.3	15.5	
	2	11.7	7.3			
	3	12.7	7.9			
	4 (resonated)	12.6	7.8	16.1	17.7	
Autoclaved bone from benign sclerosing osteitis of tibia: two hours at twenty-seven-pounds, blended	1	11.5	7.15			
	2	12.9	8.05			
Autoclaved bone: four hours at twenty-seven pounds, blended	1	5.59	3.5			E.M. 3
	2	5.49	3.4			
	3	6.20	3.88			
	4	6.48	4.05	17.3	17.3	
Glycol-ashed bone	1		0.0	18	**	E.M. 19

* 25–50: Average over thirty in several experiments on subepiphyseal and subperiosteal bone[66].

** 6–18: Average about thirteen in several experiments on glycol-ashed bone[66].

active phosphorus.[94,95] Table VII gives data on the exchange of radio-active phosphorus as worked out by Neuman on blended, autoclaved, and glycol-ashed bone. Table VII also gives values for protein nitrogen in fresh, blended, and autoclaved bone. Bone samples blended, blended and resonated, and blended with hyaluronidase, all show the phosphorus exchange of fresh bone. Autoclaved bone and glycol-ashed bone behave differently, failing to show as much phosphorus exchange as fresh bone. Since a considerable, although definitely decreased, exchange takes place in samples free of organic material (such as glycol-ashed bone), the process of calcium and phosphorus exchange in fresh bone is believed due partly to the presence of inorganic crystals and partly to the

presence of the organic component. A certain amount of the calcium and phosphorus at any moment is probably in a non-crystalline, diffusible form, in the cement substance, in fresh bone. This is particularly obvious when the concept of continuous exchange of atoms in living bone is considered. Therefore, after bone-preparation methods such as glycol-ashing, which remove the organic matrix (the cement substance and collagen) and also the calcium, phosphorus, sodium, magnesium, citrate, and carbonate ions diffused in this gel-like organic phase which normally surrounds the crystals, the only atoms available for exchange are those in the crystal periphery. It is not necessary for the crystal size or shape to change in order to have a difference in exchange rates of radioactive phosphorus between fresh bone and bone from which the organic matrix has been removed by methods involving temperatures below 400 degrees centigrade. Since temperatures over 38 degrees centigrade were not used in the blending method, or over 143 degrees centigrade in the glycol-ashing and autoclaving methods, it is concluded that these methods of bone preparation for the electron microscope did not alter the size or shape of the inorganic crystal. Proof of this is offered in the electron micrographs.

METHOD

The electron microscope * has a resolving power which allows one to view objects as small as 20 Angström units in length. Since x-ray diffraction studies suggested that bone crystals are in the range of 10 to 10,000 Angström units, efforts were made to visualize the inorganic bone crystals in the electron microscope.

Methods of preparing bone for these studies were published by Robinson and Bishop [109]. The thought behind development of these methods was to separate bone mechanically into the individual bone crystals, or into small blocks of bone crystals so that these could be placed on the specimen screen of the electron microscope without undergoing physical alteration.

The lower theoretical crystal length is set by the longest dimension of a hydroxyapatite unit cell, or about 16 Angström units. The lower limit of any crystal length as observed in the electron microscope is determined by the resolving power of the electron microscope, optimally 20 Angström units.

After whittling small slivers of fresh bone into distilled water, the investigators placed the mixture in a Waring Blendor for ten minutes. The mixture was chilled so that the blending did not cause heating of the bone. A drop of the resulting cloudy fluid was then placed in the vacuum chamber of the electron microscope; the air was evacuated and the electron beam was directed through the specimen. The image was then viewed on a small fluoroscopic screen. When a field of a specimen was found to be of interest, it was photographed.

Autoclaving or glycol-ashing was found necessary in order to remove cement substance and collagen fibers when one wished to get the sharpest definition of the bone crystals. Blending and ultrasonics at 400 kilocycles were found particularly useful in dispersion of the crystals after the organic matrix had been removed.

After visualizing the inorganic bone crystals, it seemed that, with modification of these techniques and use of various types of bone, the spatial relationship of the crystals to the collagen fibers of bone could be demonstrated by use of the electron microscope.

Tooth samples have been studied in the electron microscope, both by pulverizing dentine [42] and enamel [18] and by colloidin replica technique of polished and etched surfaces of tooth [41,43,108] and bone [44]. Replicas of the surface of etched bone have been photographed in the electron microscope by Gerould (E.M. 29).

Boyle and his associates discussed the electron-diffraction patterns of enamel crystals from the developing teeth of a guinea pig. They could not differentiate fluorapatite and hydroxyapatite by this method. They also noted that Gerould reported direct examina-

* R.C.A. type "E.M.U." electron microscope was used.

tion of pulverized tooth in the electron microscope in 1945, but that description of the appearance of the crystalline units of enamel had not been made prior to their report. The micrograph which they described was published by Orban [97]. No electron micrographs of the individual inorganic crystals of bone have been found in the literature prior to those shown in the paper by Robinson and Bishop [100].

Criticism of the Blending Method of Bone-Sample Preparation

The point might be raised that blending bone causes tiny fractures in the crystalline material. This is unlikely since much larger hydroxyapatite crystals, such as enamel and synthetic crystals, failed to break up to the size of the crystals seen in bone during the same treatment. Actually, blending is a rather gross treatment when one considers the size of these inorganic particles. The large blade of the Waring Blendor would not be likely to contact a single small crystal in such a way as to break it in two.

The method might be criticized because it tends to break the bone into small parts in such a way that the pattern of the bone as it exists *in vivo* is destroyed. This criticism, however, is considered relevant only if one were to draw conclusions involving the total pattern of a bone. Actually, in this report we are drawing conclusions in regard to the individual crystals and their grouping at a very low level of organization. Once the elements of bone can be seen and oriented at the level of 10 to 10,000 Angström units, then the electron microscope may be used to unify the whole picture by replica techniques or thin tissue sections. Exploratory work on this type of bone and tooth preparation has been started by Gerould (E.M. 29) [43].

CORRELATION OF ELECTRON MICROSCOPIC FINDINGS WITH DATA OF OTHER INVESTIGATIONS OF INORGANIC BONE CRYSTALS

1. *The Unit Cells*

The unit cell of the inorganic hydroxyapatite crystals of bone has a size and shape. The volume of the unit cell is the space occupied by these atoms $Ca_{10}P_6H_2O_{26}$ when they are arranged as hydroxyapatite [88, 92] (Figs. 1-A, 1-B, and 1-C). The dimensions of the *A* and *C* axes used for the calculations are as given in Figures 1-A, 1-B, and 1-C:

A. Area of one of four rectangular faces of the unit cell: 6.5×10^{-15} cm.^{2}.

B. Area of one of two quadrilateral faces of a unit cell: 7.7×10^{-15} cm.^{2}.

C. Area of unit cell of hydroxyapatite bone crystal: 41.6×10^{-15} cm.^{2}.

D. The volume of the unit cell may be obtained by using formula suggested by Mehmel [88]:

1. $$V = \frac{a_o^2}{2} \times \sqrt{3} \times Co$$

wherein a_o = *A* axis of unit cell
and C_o = *C* axis
V = 534 cubic Angström units.

2. This can also be obtained by the following calculation:
$(7.7748 \times 10^{-15}$ cm.$^2) \times (6.88 \times 10^{-8}$ cm.$) = 534 \times 10^{-24}$ cm.^{3} = volume of one unit cell.

E. Since there are 1×10^{24} cubic Angström units in a cubic centimeter, this number divided by the volume of a unit cell gives the number of unit cells theoretically possible in a hydroxyapatite crystal with a volume of one cubic centimeter.

$$\frac{1 \times 10^{24}}{534 \times 10^{-24}} \text{ cubic Angström units} = 1{,}869 \times 10^{18}$$

F. The theoretical specific gravity of hydroxyapatite can also be calculated on the atomic structure of the unit cell by the method Mehmel [88] and Nacken [92] used to calculate the specific gravity of fluorapatite:

Atoms	Number of Atoms per Unit Cell	Atomic Weight	Relative Weight per Unit Cell	Factor × Relative Weight per Unit Cell = Total Molecular Weight of Unit Cell
Ca	10	40.080	400.80	2.506 (+) = Ca factor
H	2	1.008	2.00	
P	6	30.980	185.88	5.405 (+) = P factor
O	26	16.000	416.00	

Total molecular weight of unit cell = 1,004.68

Avogadro's number, representing the number of molecules in a gram-molecular weight of a substance and also the number of atoms in a gram-atomic weight of an element, has been calculated as 6.0228×10^{23}. Therefore, the weight of one unit cell is calculated as follows:

$$\frac{\text{Molecular weight of unit cell}}{\text{Avogadro's number}} = \frac{1{,}004.68}{6.0228 \times 10^{23}} = 1.6 \times 10^{-21} \text{ grams per unit cell.}$$

The specific gravity of the hydroxyapatite unit cell is then calculated as follows:

$$\frac{\text{Weight per unit cell}}{\text{Cubic centimeter volume per unit cell}} = \text{specific gravity or } \frac{1.6 \times 10^{-21}}{0.53 \times 10^{-21}} = 3.01$$

or approximately 3.0 is the specific gravity of a hydroxyapatite unit cell.

G. A theoretical calcium-phosphorus ratio of the hydroxyapatite atomic lattice can be calculated as 2.156(+), or approximately 2.16.

H. Since the specific gravity of hydroxyapatite is about 3.0, *the volume of one gram of hydroxyapatite bone crystals should occupy only 0.33 cubic centimeter.*

I. The number of unit cells in a cubic centimeter of hydroxyapatite was calculated as $1{,}869 \times 10^{18}$. Since 0.33 cm.^{3} contains one gram of hydroxyapatite, then *one gram of hydroxyapatite contains 620.3×10^{18} unit cells.*

II. *The Crystals*

A. After measuring 1,000 crystals of human bone, the average dimension arrived at was, in round numbers, $500 \times 250 \times 100$ Angström units. The following data concerning such a crystal were calculated:

1. Surface area of 40×10^{-12} cm.^{2}.
2. Volume of 12.5×10^{-18} cm.^{3}.
3. Unit cells per crystal: 23,400.
4. Number of crystals per gram: 2.65×10^{16}.
5. Surface area of one gram of such crystals: 106 square meters.
6. Outermost atomic layer contains, in proportion to all atoms of the crystal, about 12 to 14 per cent. of the atoms.

The following data, calculated for a tabular hydroxyapatite crystal $500 \times 250 \times 150$ Angström units are also listed:

1. Surface area of 47.5×10^{-12} cm.^{2}.
2. Volume of 18.25×10^{-18} cm.^{3}.
3. Unit cells per crystal: 34,830.
4. Number of crystals per gram: 1.78×10^{16}.
5. Surface area of one gram of such crystals: 84 square meters.
6. Outermost atomic layer contains, in proportion to all atoms of the crystal, about 9 to 10 per cent. of the atoms.

B. *The surface of a bone crystal as the site of gas adsorption:* Wood measured the surface area available for adsorption of nitrogen gas at low pressures and low temperatures on samples of glycol-ashed, powdered rabbit bone as 99.3 square meters per gram; on synthetic apatite as 51.1 square meters per gram; and on enamel as 1.8 square meters per gram.

TABLE VIII

GLYCOL-ASHED BONE EQUILIBRATED WITH PHOSPHATE BUFFER (P^{32} = 83 γ/c.c.), pH 7.5
PERCENTAGES OF EXCHANGE

0 Degree Equilibrating Temperature			37 Degrees Equilibrating Temperature	
E. M. 19: Specimen	E. M. 20: Specimen	Days (*Number*)	E. M. 19: Specimen	E. M. 20: Specimen
8.6	0	1	10.3	0
11.3	0.1	3	16.5	0.09
12.6	1.5	6	18.0	0.5
12.2	0.6	12	22.0	2.7

Hendricks and Hill [56] measured the surface area of steamed cattle bone by gas adsorption studies as 68.7 square meters per gram (E. M. 5). There was some organic matter remaining on the steamed cattle bone crystals. The presence of such organic material apparently hinders gas adsorption but tends to increase the exchange of calcium and phosphorus ions. After removal of practically all the organic material, Hendricks concluded the surface area is 80 to 100 square meters per gram for the inorganic crystals.

From the calculations presented above (that is, that one gram of hydroxyapatite crystals of bone has a surface area of about 85 to 106 square meters) we feel that the gas adsorption studies tend to support the electron microscopic observations of the crystal size. Hodge [66] assumed that the crystalline material of bone had a specific gravity of 2; he also assumed that the crystals were cubes of about 300 Angström units along one edge. Such crystals would have a surface area of 100 square meters per gram. However, it has been shown above that the specific gravity of hydroxyapatite crystals should be about 3 instead of 2. With flotation methods using 60-mesh powder, the porosity probably accounts for the lower value of 2.82. Enamel crystals which are also hydroxyapatite but which are much more densely packed give a specific gravity of 2.9 by the same flotation method.

If the theoretical value of 3 is used and if one assumed that inorganic crystals of bone were cubes, such crystals would then have to have a length of 200 Angström units on a side, if the surface area per gram were to be 100 square meters. Therefore, the gas adsorption studies on bone crystals and specific gravity of hydroxyapatite are compatible with a cubic crystal 200 Angström units on a side, but the electron micrographs show that the crystals are not cubic. Therefore, such gas adsorption data must be referred to tabular crystals (Fig. 1-D).

C. *The surface of a bone crystal as the site of calcium and phosphate ion exchange:* From studies with radio-active calcium and phosphate, in which glycol-ashed bone was used, it has been calculated that approximately 10 to 12 per cent. of the calcium and phosphorus atoms in the bone crystals are readily exchangeable [66,93]. Since the exchange phenomenon is reduced by increasing the crystal size (enamel crystals as compared with bone crystals), it is assumed that only those atoms in the outer layer of the crystal at any given moment are available for immediate exchange of calcium and phosphorus atoms [73,94]. The thickness of the exchangeable atomic layer on a crystal is believed to vary somewhat with the experimental temperature (Table VIII). Therefore, calculation of the number of calcium and phosphorus atoms in the surface layer of a crystal compared to the number of these atoms in all the unit cells of a tabular crystal 500 Angström units long by 250 Angström units wide by 100 Angström units thick were made. About 24 per cent. of the unit cells of such a crystal contact the surface of the crystal by such calculations. Since each unit cell contains two molecules, there will be approximately 12 to 14

per cent. of the hydroxyapatite molecules, or 12 to 14 per cent. of the atoms of the whole crystal, on the surface layer. In other words, about 12 per cent. of the calcium and phosphorus atoms of the whole crystal are on the surface and these atoms, due to their peripheral position, are available for exchange. These calculations are based on crystals from which the surrounding cement substance was removed by prolonged steaming, autoclaving, or glycol-ashing. As will be pointed out in the following discussion, studies of the exchange of radio-active atoms and of gas adsorption are markedly altered as soon as the cement substance of fresh bone is introduced into the picture. The surface of a crystal in the fresh state is covered with cement substance. When this cement substance is present, an "aura" of diffusible atoms is believed to appear in it around the crystal; and ion-exchange values based on exchange experiments with radio-active calcium and phosphorus rise sharply. The gas-adsorption values in fresh bone, on the other hand, fall sharply, since the cement substance covers the crystal faces and is thought to prevent nitrogen-gas adsorption on the crystal surfaces.

D. *The surface of a bone crystal as the site of carbonate, citrate, magnesium and sodium ions:* Hendricks and Hill [56] base arguments on the following four groups of experimental data:

"1. A single phase having the x-ray diffraction pattern of apatite and containing carbonate is present even though bone forms in a system unsaturated with respect to calcium carbonate.

"2. In human bone this phase is shown by analysis to be a neutral substance. It is more basic, approaching hydroxylapatite, in parts of enamel.

"3. A large portion of the carbonate in bone can be preferentially removed by solution in acid without destruction of the apatite lattice. Enamel and some 'carbonate apatites' dissolve uniformly.

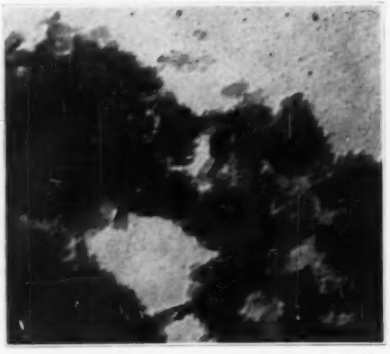
"4. Citrate is present in bone as water insoluble form in amounts by volume approaching one-half that of carbonate."

The first and third groups of data listed by Hendricks and Hill "indicate rather clearly that carbonate is on the surface of the bone material. Presence of citrate can also be explained in this way instead of being merely 'adventitious.' Bone also contains magnesium and sodium that might be expected to replace Ca ++ in the apatite structure on the basis of ionic radii for Na + and Mg ++. These two are preferentially dissolved by acid, however, indicating their location on the lattice surface" and not in the depth of the crystal lattice.

Hendricks and Hill proceed to show that the surface area of the crystalline phase of a bone sample can be roughly calculated from the carbonate content of the sample. They previously suggested that there are about 7.5×10^{20} CO_3 groups per gram of bone crystals and that each CO_3 group probably occupied 13.3 square Angström units or 13.3×10^{-16} square centimeters on the surface of a bone crystal.[55] Calculations of bone crystal surface area on the basis of carbonate tally well with calculations based on electron micrograph studies. For instance, according to the calculations based on the electron micrographs, there are 2.65×10^{16} crystals ($500 \times 200 \times 100$ Angström units) per gram of bone crystals. Each one has a surface area of 40×10^{-12} cm.^{2}. Therefore, $(40 \times 10^{-12}) \times (2.57 \times 10^{16}) = 106 \times 10^4$ cm.^{2} per gram, and $\frac{106 \times 10^4}{13.3 \times 10^{-16}} = (7.9 \times 10^{20})$ CO_3 groups per gram.

E. *Calculations to show that all the calcium in bone is not in crystalline form:* Hendricks and Hill [58] have pointed out that *calcium* carbonate can be preferentially dissolved from bone. With other data, this is the basis for his argument that the carbonate is attached to the crystal surface. They further state [56] that, if even one-third of the carbonate present in bone were in the crystalline form of calcite, it would be distinguishable from the hydroxyapatite by methods using a Geiger counter x-ray spectrometer. Several investigators have made a third point,—namely, that excess phosphate ions probably occur on the sur-

E. M. 1



E. M. 2

E. M. 1: *Fresh bone (cortex) from the distal portion of a human rib, blended in distilled water:* A drop of the cloudy fluid resulting from the blending of rib in water was placed on the specimen screen of the electron microscope and the field was photographed at a magnification of 3,760 × in the electron microscope and then enlarged to 18,500 × photographically. At this magnification, details of the crystalline elements are not good, but one does obtain a general picture of inorganic crystals held in the cement substance and encrusting the collagen fibers. Periodic banding of some portions of these fibers at about 640 Angström units is seen in at least two of the extensions of the main mass. This periodicity is typical of that seen in collagen fibers [38, 40, 107]. However, in this case the pattern is made visible by the relative density of the crystalline deposits on the fibers rather than phosphotungstic acid-staining.

E. M. 2: *Fresh bone from the cortex of a human metatarsal:* The crystalline material was more clearly visible since the magnification was 34,500 ×. The crystals were still closely bound in the cement-substance matrix, and only at the periphery of the block could one occasionally observe a single inorganic bone crystal. Blended cortex of comparatively rigid bone such as a metatarsal showed a closer packing of the inorganic crystals and fewer crystal-encrusted collagen fibers were seen than in blended cortex of more flexible bone, such as rib. (Most of the protein polysaccharide complex of fresh cement substance is usually alcohol and water insoluble.[45])

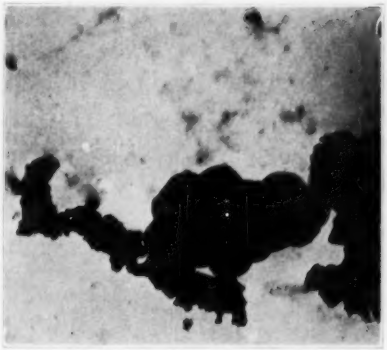
face of the bone crystals separate from those in the lattice of hydroxyapatite crystals. The conclusion to be drawn is that a certain amount of the calcium and phosphate exists in a non-crystalline form external to the crystals.

When one uses the phosphorus factor mentioned above and multiplies the phosphorus in bone samples as analyzed by Vogt and Toensager [119], a figure is arrived at which gives grams of hydroxyapatite crystals. This assumes for the moment that all of the phosphate in 100 grams of bone is in the crystals. Thus: 8.05 grams of phosphorus per 100 grams of hydrated bone (marrow removed) × phosphorus factor 5.405 = 43.5 grams of hydroxyapatite crystals.

If one then multiplies the calcium in bone as analyzed by Vogt and Toensager [120] by the calcium factor noted above, one obtains the number of grams of hydroxyapatite crystals that could be made with the total calcium available in the sample. Thus: 18.72 grams of calcium per 100 grams of hydrate bone (marrow removed) × 2.5066 (calcium factor) = 55.9 grams of hydroxyapatite crystals.

It is apparent that the calcium available would make many more hydroxyapatite crystals than it would be possible to construct with the amount of phosphorus present. Having made these calculations, one must then note that bone protein contains the order of 0.2 per cent. phosphorus [14]. Further, phosphate is not all in the crystal lattice or in the protein but some may be present as diffusible phosphorus about the crystal surfaces in the cement substance as *excess phosphate*. These considerations force one to reduce the number of phosphate ions that were first assumed in the calculations above to be available for hydroxyapatite formation: as a result, the number of calcium ions that can possibly occur in the hydroxyapatite crystals of bone is further reduced. Table I was constructed on the basis of these considerations and shows that 2 to 3 grams of the 17 grams of cal-

E. M. 3



E. M. 4

E. M. 3: *Human cortical bone:* This bone had been autoclaved at twenty-seven pounds for two hours, blended for ten minutes, re-autoclaved for two hours, and blended again for ten minutes (Magnification 34,500 ×). One micron = 10,000 Angström units = 3.45 centimeters; or 1 millimeter = 293 Angström units. Prior to observation in the electron microscope, a water suspension of the sample was subjected to ultrasonics at 400 kilocycles for ten minutes. Various crystals were measured and the following rather typical measurements were obtained:

Length (*Millimeters*)	=	(*Angström units*)	×	Width (*Angström units*)	×	Thickness (*Angström units*)
2 7	=	780	×	350	×	—
1 2	=	350	×	—	×	100
2	=	580	×	290	×	—
8	=	230	×	—	×	80
5	=	1450	×	—	×	150
5	=	1450	×	800	×	—
2	=	580	×	145	×	—

The crystal length generally varied between 200 and 1,500 Angström units, and the width between 100 and 800 Angström units. Occasionally, a crystal measuring 20 Angström units or less was seen. These are at the lower limit of the resolving power of the electron microscope. The crystals all appeared to be tabular in form. In some places they showed up as particularly dense, narrow, long bodies. These are believed to be tabular crystals standing on edge on the specimen screen. This was better observed in stereopticon views. After making this assumption, the length of these long, narrow, dense bodies was measured and compared with the measurements of length of the flat-lying, tabular crystals previously obtained. The lengths were comparable. The width of these long, narrow objects ranged between 50 and 200 Angström units. These measurements are believed to represent the thickness of the crystals. These data are comparable to data obtained from the shadow-cast samples, E. M. 8 and E. M. 9.

E. M. 4: *Human bone:* This bone had been ashed in a muffle furnace at 750 degrees centigrade for one hour (See Fig. 3,*D*). Heat caused the fusing of the small crystals into large crystalline masses (Magnification 34,500 ×).

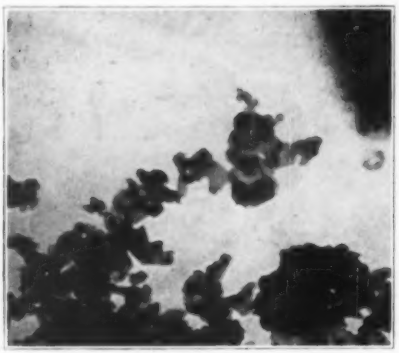
eium in every 100 grams of hydrated bone are probably not in the hydroxyapatite crystals but in the cement substance in a non-crystalline form along with the "excess and non-protein phosphorus" (0.2 ± gram), sodium (0.15 ± gram), magnesium hydroxide (0.15 ± gram), CO_2 (2.0 ± grams), and citrate (0.4 ± gram) [56].

DISCUSSION

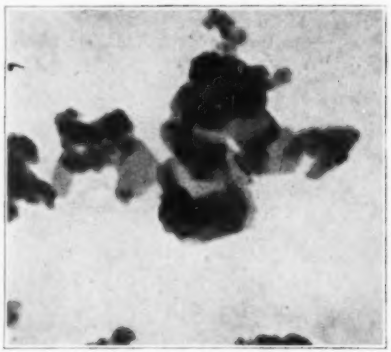
By use of the electron microscope the general dimensions and shape of the inorganic bone crystals have been demonstrated.

In Electron Micrograph 1, one observes collagen fibers covered with cement substance which is full of hydroxyapatite crystals. This is a small fragment of fresh bone.

Electron Micrograph 2 shows a similarly prepared piece of human metatarsal. This is at about twice the magnification of Electron Micrograph 1. Here a few of the individual hydroxyapatite crystals can be seen at the periphery of the crystal-cement substance masses. This bone is less flexible than the rib and the collagen fibers are not so obvious.



E. M. 5



E. M. 6

E. M. 5: *Steamed cattle bone, blended* (Magnification 36,600 ×). Some of the crystals appeared to have a definite hexagonal outline.
E. M. 6: A small section of E. M. 5 (Magnification 100,000 ×).

By autoclaving bone at twenty-seven pounds of pressure for four hours it is possible to remove *most* of the organic matrix without changing the size or shape of the inorganic crystals. The bone crystals separated from the organic matrix are clearly seen in Electron Micrograph 3.

Electron Micrograph 4 shows crystals of the cortex of the femur of a mature cow, cleared of most of the organic matrix by prolonged steaming. Steaming is similar to autoclaving since it converts collagen to gelatin. The gelatin and cement substance become less viscid and flow away from the bone crystals into the water bath. Hendricks found that the gas adsorption of this particular material was such that a gram of these crystals had a combined surface area of 68.7 square meters. It should be noted that a small percentage of organic matter remains in this specimen and blocks gas adsorption on some crystals. Crystals totally free of organic matter give 80 to 100 square meters of surface area per gram with gas adsorption methods. One part of this micrograph has been enlarged. In Electron Micrographs 6 and 7 are seen the mature crystals with hexagonal outlines. Studies with radio-active tracers and the determination of water content of such cortical bone show both less water and less ionic exchange. These crystals from cortical bone are therefore believed to have resided in a more stable matrix and thus have assumed their ultimate crystal form.

Bone crystals appeared to be tabular or "book-shaped". To prove that they were tablets (and not cubes or rods) a dispersed sample was photographed (E. M. 8), removed from the electron microscope, shadow-cast with uranium, and placed back in the microscope. The result is observed in Electron Micrograph 9. Since the uranium shadow was cast onto the slide at a 15-degree angle of incidence, the shadows are about three and one-half times as long as the thickness of the object casting the shadow. By this method it has been demonstrated that these bone crystals are tabular in shape and hexagonal in outline in their most well developed form. From these facts, Figure 1-D was drawn to represent a bone crystal. The bone crystal is broken down into unit cells in Figure 1-E to show how the lattice of calcium, phosphorus, and hydroxyl groups is believed to lie in relation to the crystal. The *A* and *C* axes are shown.

By measurement on electron micrographs of controlled magnification, the *average dimensions of the inorganic crystals in human bone* were about 500 × 250 × 100 Angström units. A gram of such crystals can be calculated to have an area of 102 square meters. It can also be calculated that approximately 12 per cent. of the calcium, phosphorus, and hydroxyl units in the lattice making up such a crystal lie in the crystal periphery. Such a

peripheral position would at least appear to facilitate atomic exchange with a suitable surrounding menstruum.

These calculations check well with:

A. The bone-crystal size suggested by x-ray diffraction (10,000 to 10 Angström units) although by electron micrography the upper limit was reduced to 1,500 Angström units).

B. Gas-adsorption studies which show that a gram of bone crystals have 80 to 100 square meters of surface area.

C. Exchange studies with radio-active phosphorus which show that inorganic bone crystals from which the organic matter has been removed, when in equilibrium with a synthetic "plasma" in the test tube, have 6 to 18 per cent. of their phosphorus atoms readily available for exchange, the average exchange under these conditions being 13 per cent. Calculations on the basis of electron micrographs suggest about 12 per cent.

D. Hendricks's carbon dioxide surface area calculations for bone crystals, although this factor probably varies somewhat with the ratio of carbonate to phosphate.

The crystals appear in the cement substance of the matrix and not in the collagen fibers. This is particularly well demonstrated in Electron Micrographs 10, 11, and 12.

It has already been noted that the bone cell, like any well differentiated derivative of reticulum cells, creates a characteristic matrix.

The derivatives of the mesenchyme, or of the reticulum cells, in the adult have one common denominator in the matrices they create,—the collagen fibers. However, these fibers are not the element in the various matrices created by these cells that differentiates them from each other [40].

The derivatives of the reticulum cells create in their extracellular matrix not only collagen fibers but cement substance or ground substance. This cement substance apparently accounts for the site of formation of hydroxyapatite crystals in bone, the typical size and shape of bone crystals, the rate and amount of atomic exchange of calcium, phosphorus, and other inorganic constituents between the bone and extracellular fluid, and certain structural characteristics of bone.

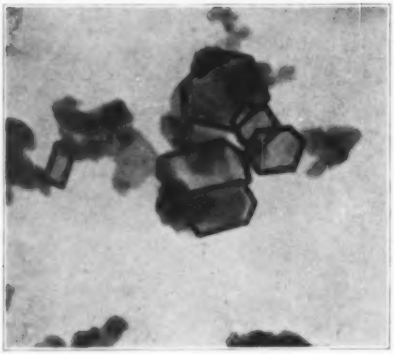
Histologists using histochemical techniques have noted a difference in cement substances and have gone so far as to suggest that, when a cement substance stains in a characteristic way with metachromatic dyes, one may suppose that that matrix is destined to become calcified.

However, the cement substance of bone matrix is probably different from that of other calcifying connective tissues. This difference is not directly visible in the electron micrographs. However, the crystals that form in the matrix laid down by the ameloblast which forms tooth enamel are much different in size and shape from bone crystals (E. M. 13 and E. M. 14). They appear to be 400 to 600 Angström units wide, 100 to 200 Angström units thick, and several thousand Angström units long (10,000 Angström units). They are arranged in fascicles to make up the enamel rods. There is also evidence by electron diffraction that these crystals are long flattened hexagonal rods, with the *C* axis of the unit cell in the long axis of the crystal, whereas in bone the crystals are tabular in shape and the *A* axis may lie in the long axis of the crystal. Both bone and enamel crystals are hydroxyapatite.

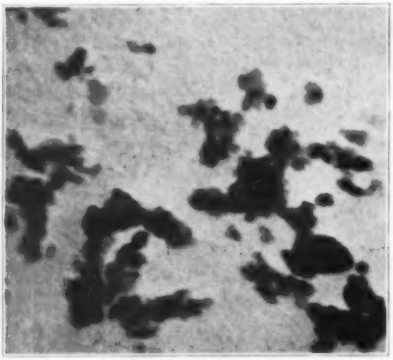
Brandenburger and Schinz noted on the basis of x-ray diffraction data that, whereas most normal and abnormal calcifications in man were hydroxyapatite, *the crystal size* seemed to vary, depending on the matrix in which the crystals formed (Table VI).

A further point to substantiate this size variation is given by electron micrographs of hydroxyapatite crystals formed in a test tube. By controlling the solution, relatively larger (E. M. 15) or smaller (E. M. 16) crystals may be obtained.

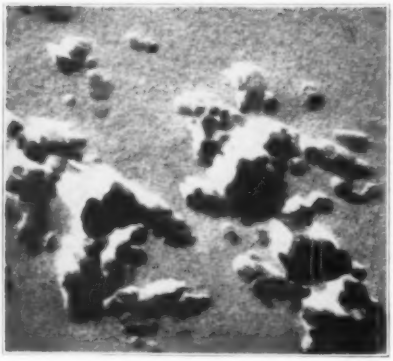
The hydroxyapatite crystals in a supraspinatus-tendon calcification (E. M. 17) are about the same length as bone crystals *but are needle-shaped instead of tabular as in*



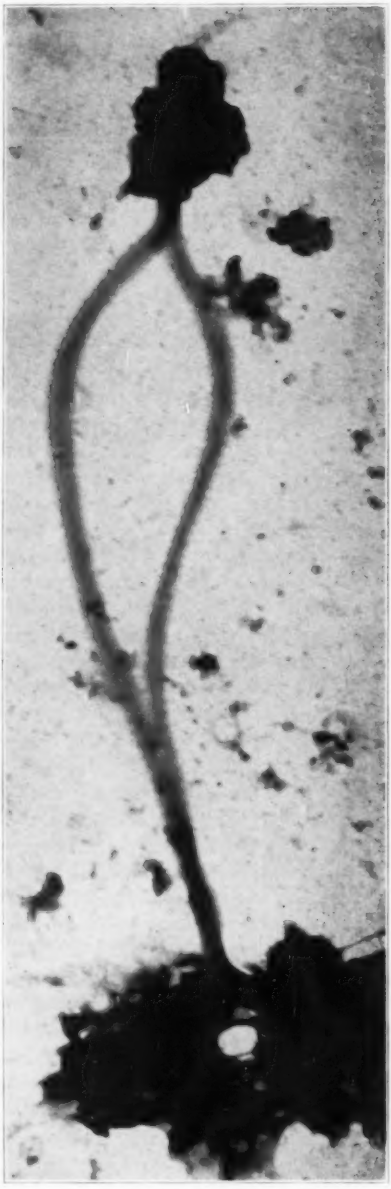
E. M. 7



E. M. 8



E. M. 9



E. M. 10

E. M. 7: Crystals noted in E. M. 5, outlined. Such crystals were used as the pattern for Fig. 1-C (Magnification 100,000 ×).

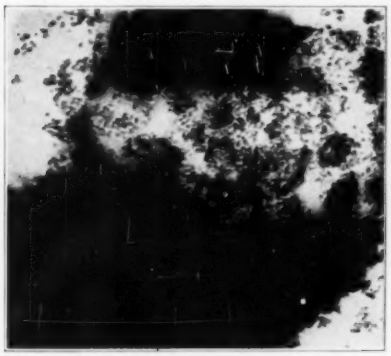
E. M. 8: *Autoclaved and blended human bone:* The bone has been well dispersed by resonating at 400 kilocycles for ten minutes (Magnification 34,500 ×).

E. M. 9: Identical Field to that seen in E. M. 8 (Magnification 34,500 ×): The surface of the speci-

(*Continued on on page 417*)

men screen was shadowed with uranium so that the uranium particles hit the screen at a 15-degree angle of incidence. In this way the shadow was made relatively long in relation to the height of the object that casts the shadow. At 15 degrees, the shadow is approximately three and one-half times as long as the height of the object casting the shadow (that is, co-tangent of angle 15 degrees = 3.58). Single crystals appear to have a thickness of about 50 to 200 Angström units, averaging around 100 Angström units, whereas groups of crystals which completely obstruct the electron beam appeared to be 400 Angström units or more in thickness.

E. M. 10: *Bone, senile, cortical, blended* (Magnification 34,500 ×): Preparation stained with phosphotungstic acid, 0.001 per cent. for one hour. The collagen fibers were seen to emerge from the cement substance which surrounded them at either end. As is characteristic of collagen, these fibers stained darkly at about 640-Angström unit intervals. In this cement substance lay darker masses of inorganic crystals. The crystals were not clearly seen because of the presence of the cement substance which had retained some of the phosphotungstic dye and had thus become more electron-opaque than is usual. It will also be noted that, where this cement substance formed a sheath about the collagen fibers, the striations were no longer visible. Where the fibers were free of both cement substance and crystals, the periodic pattern typical of collagen fibers was seen. It was noted that the bone crystals of senile and infantile bone (E. M. 28) separated easily from the collagen fibers during mechanical agitation (that is, blending). This was not true of young adult bone (E. M. 21).



E. M. 11

E. M. 12

E. M. 11: *Fresh blended bone from cortex of femur of rabbit* (enlarged 18,500 ×): The masses were made of inorganic crystals in the enveloping cement substance. The inorganic crystals in certain areas could be seen lying separately from the large masses.

E. M. 12: *Fresh blended bone from cortex of rabbit femur:* This bone had been incubated with hyaluronidase at pH 7.3 for two hours (Magnification 18,500 ×). The masses of crystals were separated into small clumps in the apparently "swollen" cement substance; because of the presence of large amounts of cement substance, the separate inorganic crystals were not clearly defined.

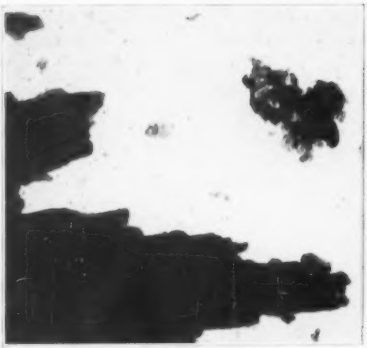
bone. Calcifications in the subcutaneous tissue of the fingers from a subject with a calcinosis localisata lesion show typical crystals. They are needle-shaped or boat-shaped but are much larger than crystals in bone. They, too, are hydroxyapatite (E. M. 18) (Table IV).

By electron micrographs we have demonstrated visually that not only does the crystal size of hydroxyapatite vary in different matrices, but crystal shape also varies.

The radio-active phosphorus exchange figures not only check with the surface calculations of the bone crystals from which organic matter has been removed, but they also check with the crystal size found by electron micrography after bone crystals are heated in excess of 400 degrees centigrade (E. M. 3, E. M. 4, E. M. 19, and E. M. 20). In the latter preparation the crystals are still hydroxyapatite. In fact, they give sharper x-ray diffraction patterns because they are larger and the atomic reflection planes of their lattice are larger (Fig. 3,*D*). They are simply a fusion of many small crystals. As can be seen in Table VIII, the radio-active exchange drops as the crystals enlarge and the surface area becomes simultaneously diminished.

Up to this point the inorganic crystal as a separate entity has been discussed. In *orthopaedic surgery*, one deals with the bone crystal in relation to the bone matrix.

The presence of matrix entirely changes the data of radio-active tracer exchange.



E. M. 13

E. M. 14

E. M. 13: *Normal deciduous tooth, autoclaved and blended* (Magnification 34,500 ×): A fascicle of the long crystals forming an enamel rod was seen. The width of the crystals is about 400 to 600 Angström units, the thickness about 100 to 200 Angström units. It is assumed on the basis of shape and of related data [11, 12, 18, 106, 114] that these were long, flat, "ribbon-like" crystals, hexagonal in cross section; the *C* axis of a unit cell of the crystals was lying in the long crystal axis. These are much larger crystals than ever occur in bone. An electron micrograph of similar enamel crystals, not, however, arranged in a rod, has been previously observed [97].

E. M. 14: *Normal deciduous tooth, blended* (Magnification 34,500 ×): Separate crystals of an enamel rod were more dispersed in this field. The smaller crystals from the dentine and interprismatic areas were also seen. The blending method of itself does not create crystals of the uniformly small size occurring in bone samples. Dentine crystals are about the size of bone crystals according to x-ray diffraction data.

E. M. 15

E. M. 15: *Synthetic hydroxyapatite* (Magnification 20,500 ×): Tabular forms were seen. The crystals, in contrast to those in E. M. 16, had a "pebbly" irregular surface. (Description of this preparation can be found in Reference 68, Preparation T-1.) Excess adsorbed phosphate was found in this preparation.

For instance, in Table VII it was noted that in fresh bone the equilibrated radio-active exchange of phosphorus was much higher than in bone from which the organic matter had been removed (25 to 30 per cent. instead of 6 to 18 per cent.). Nevertheless, in Electron Micrograph 21, the inorganic crystals (seen here encrusted about collagen fibers) appear to be the same general size in fresh bone as in bone from which organic matter has been removed (E. M. 3). Some factor other than crystal size apparently causes the more rapid exchange.

Furthermore, the exchange of radio-active phosphorus with samples of forming bone from the subperiosteal and subepiphyseal area has been found to be very large (35 to 50 per cent.).

Therefore, the crystals in subepiphyseal bone were observed. The crystal size was found to be comparable to that in mature bone of the same animal (E. M. 5 and E. M. 22). Although the crystals were a little less regular in outline and tended to be a little thinner in the subepiphyseal bone, there was no major dimensional difference to account for a difference of 75 to 100 per cent. in ion exchange.

It is reasonable to conclude that the inorganic crystal size was not the major factor which increased phosphorus exchange in fresh bone.

There are six points that suggest that the matrix, particularly the cement substance, is the factor in fresh bone which increases the radio-active phosphorus exchange. *One*

point that stood out was the larger amount of *organic matter* and *water* in *newly* formed bone. There is general agreement on this point. The *second point*, arrived at by the author by means of mathematical methods in relation to careful chemical analyses by other investigators, was that the crystals could not contain all the calcium found in a gram of

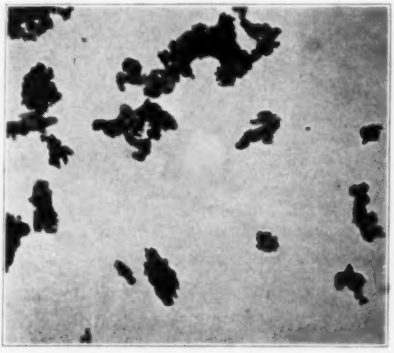
E. M. 16

E. M. 17

E. M. 16: *Synthetic hydroxyapatite* (Magnification 29,600 ×): These crystals tended to be needle-shaped and larger than the crystals usually seen in bone. A tabular form was occasionally observed. (Description of this hydroxyapatite can be found in Reference 68, Specimen TR 4.) There was no excess adsorbed phosphate. Crystals were smoother and were much smaller than those in E. M. 15.

E. M. 17: *A calcific deposit aspirated from the supraspinatus tendon in a patient with subdeltoid bursitis* (Magnification 34,500 ×): This material was blended for two minutes in distilled water and was then viewed in the electron microscope. As in the synthetic apatite (E. M. 16), the predominant habit of the crystals was needle-shaped rather than tabular. On x-ray diffraction these deposits had appeared to be hydroxyapatite. It is obvious from the illustration and the consideration of the specimen preparation that, whatever organic material might have surrounded these crystals, it did not hold them tightly together as would the cement substance about bone crystals. Furthermore, the background of the electron micrographs was uniformly cleaner than one usually obtained with simple blending of fresh bone. These observations point to the fact that the quality of the adherent organic matter in this sample was different from that in bone. Also, collagen fibers were not observed in these preparations despite the "clean" fields.

E. M. 18



E. M. 19

E. M. 18: *Crystals from hydroxyapatite deposit occurring in subcutaneous tissues of the finger of a patient with calcinosis localisata* (Magnification 34,500 ×): The very large size of some of the needle or boat-shaped crystals was seen as well as the great size variation of crystals.

E. M. 19: *Rabbit bone, glycol-ashed at 200 degrees centigrade:* This bone had been blended and subjected to ultrasonics at 400 kilocycles for fifteen minutes (Magnification 34,500 ×). Individual crystals and crystal groups were seen. Where these groups lay in such a manner that the transverse axes (Fig. 1-E) of their component crystals were parallel to the electron beam and perpendicular to the specimen screen, the long axes of the crystals appeared to lie parallel to one another. In other words, these crystals, when grouped together as in the interfibrillar spaces, formed a laminated structure like shale.

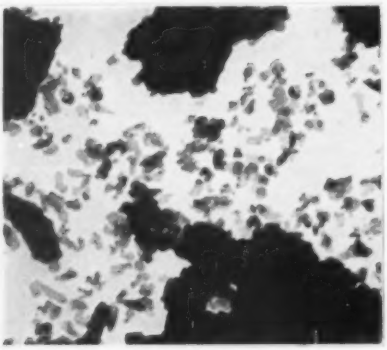
E. M. 20

E. M. 21

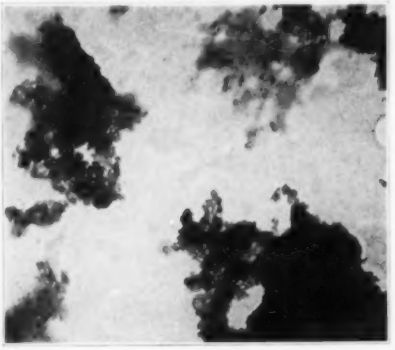
E. M. 20: *Rabbit bone, ashed at 500 degrees centigrade:* This bone showed fusion of small crystals (Magnification 34,500 ×). These larger crystals tended to have a hexagonal outline. Table VIII shows the difference in radio-active phosphorus exchange of these last two specimens of bone crystals, both free of organic matter. It is calculated from the electron micrographs that the crystals in E. M. 19 had about ten times as much surface area per gram as those in E. M. 20, and about ten times as much phosphorus exchange *in vitro*. No appreciable organic matter was present in either specimen.

E. M. 21: *Fresh bone from the cortex of the shaft of the ulna of a human, twenty-four years old, blended, unstained* (Magnification 34,500 ×). The collagen fibers were heavily encrusted with bone crystals. The crystals and their enveloping cement substance were not easily stripped from the fibers by blending, although in certain areas fibers were seen partly denuded of crystals. Crystals visible as separate entities could be seen to be of the same general size as those in the autoclaved preparations (E. M. 3). In general, the long axes of the crystals seemed to lie in the long axis of the fibers.

bone. There was not enough phosphorus to combine with all the calcium in a hydroxyapatite lattice. *Third*, it has been recently shown that although 25 per cent. of the body sodium, about 80 per cent. of the body carbonate, and a large percentage of the body magnesium are in bone, these substances are not combined in a crystalline form in bone. For instance, if even one-third of the carbonate were in a crystalline form with calcium, as had been previously supposed, it would be detectable. *Fourth*, even in bone from sub-



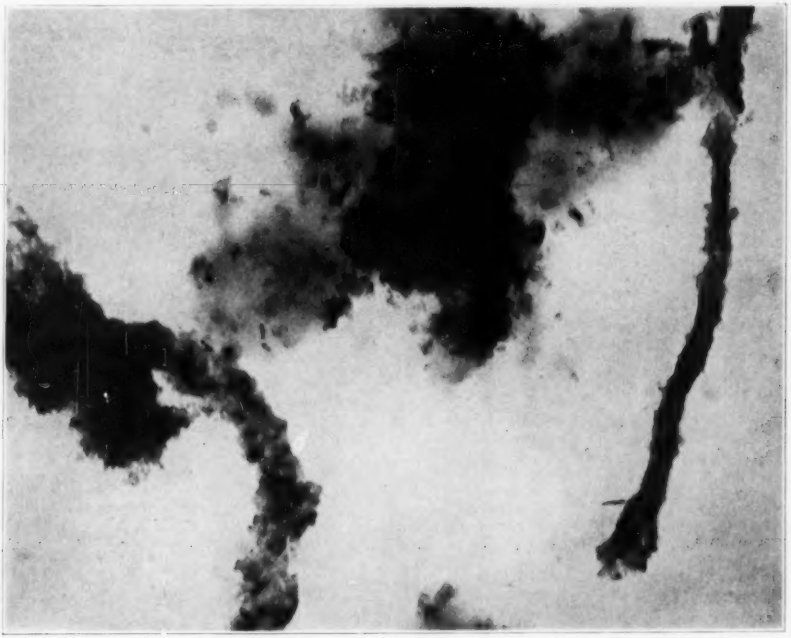
E. M. 22



E. M. 23

E. M. 22: *Cancellous new bone from subepiphyseal region of growing calf tibia:* This bone had been autoclaved four hours at twenty-seven pounds of pressure (Magnification 33,000 ×). Crystals showed the same general size as those obtained from steamed cattle bone. The crystals in veal bone appeared less regular in outline than those which were seen in mature cattle bone (E. M. 5). The average crystal size, however, was about the same as that seen in the cattle bone. Prior to autoclaving, this bone sample contained 57.2 milligrams N_2 per gram. It was obvious that part of the matrix remained in the sample, probably holding the larger masses of crystals together (Table VII).

E. M. 23: Same specimen as that shown in E. M. 22, *after being treated with dilute hydrochloric acid* (Magnification 33,000 ×). The remaining matrix was thus revealed and only those crystals embedded in the matrix escaped complete solution by the acid.



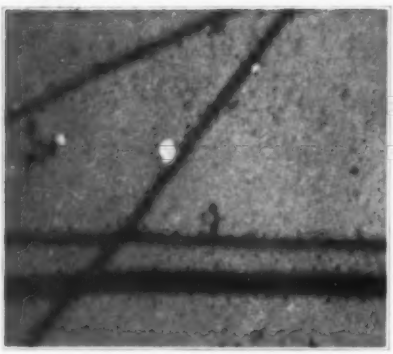
E. M. 24

Cortical human bone (rib), blended and incubated twenty minutes with hyaluronidase (Magnification 34,500 ×): Two fibers were seen encrusted with inorganic crystals. Between the two fibers there was cement substance which was apparently "swollen" by the hyaluronidase treatment. The inorganic crystalline material could be seen as electron-opaque objects in the gelatinous mass of the swollen interfibrillar cement substance. On the other hand, the crystals and the cement substance that encrusted the collagen fiber had not been markedly loosened from the fiber by the enzyme treatment. The predominantly longitudinal arrangement of the crystals about the fiber was seen.

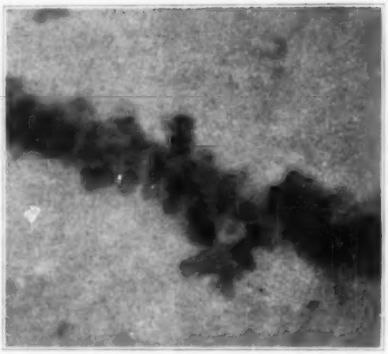
jects with fluorine poisoning, fluorine did not show in the crystalline pattern of the fresh bone. *Fifth*, these substances (sodium, magnesium, carbonate, and fluorine, when present) are differentially soluble from bone. *Sixth*, recent work by Boyd and Neuman [17] shows that the chondroitin sulphate of cartilage (chemically similar to part of the cement substance of bone matrix) has the properties of a typical cation exchange resin; also, that the cation uptake is proportional to the sulphate content of the matrix. It should be noted at this point that about 90 per cent. of the body citrate is found in bone. It has several biological properties similar to those of known cation-exchange resins when complexed with calcium [33, 46].

It would appear that the factor causing the markedly increased radio-active exchange in fresh bone, as compared with bone from which the matrix has been removed, is the cement substance which holds most of the extracellular water and contains the carbonate, sodium, magnesium, citrate, and excess calcium and phosphorus in a non-crystalline but diffusible and exchangeable form. Recent work of Hendricks and Hill [58] has added impressive evidence to this concept and has extended it by showing that the amount of carbonate is closely related to the surface area of the crystals. He conceived of the crystals as being covered in the fresh state by an aura of carbonate, citrate, sodium, and magnesium, and he suggested that the increasing concentration of these materials in the cement substance about a developing crystal may limit the size of the crystal as it forms in the bone matrix.

Bone can be considered a chemical depot. Although the skeleton comprises approximately 13 to 17 per cent. of the body weight[109], it contains in relation to the whole body



E. M. 25



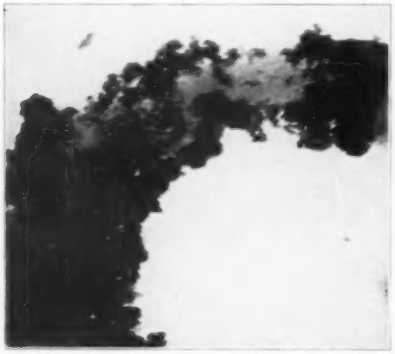
E. M. 26

E. M. 25: *Hyaline cartilage from the joint surface of a human astragalus, blended and stained* (Magnification 34,500 ×): Collagen fibers were seen and the matrix contained little electron-opaque material. In order to bring out the periodic pattern in these fibers it was necessary to stain them with phosphotungstic acid, .001 per cent., for one hour.

E. M. 26: *Cortex of human rib, blended and unstained* (Magnification 62,500 ×): The mixture was held at pH 8 by a phosphate buffer. Streptococcus hyaluronidase was added and the preparation was incubated for three hours. Periodicity along part of the crystal-encrusted collagen fiber was clearly seen. The periodically recurring bands seemed to be composed of aggregates of inorganic crystals applied at regular intervals about the underlying collagen fiber.

99 per cent. of the calcium, 25 per cent. of the sodium, a large part of the body magnesium, 85 per cent. of the phosphorus, 80 per cent. of the carbonate, and 90 per cent. of the citrate.

Radio-active tracer studies in living animals have shown that iso-ionic exchange in bone is constantly affecting a large number of calcium and phosphorus atoms[30,46,51,65,70,81]. This is more marked in cancellous bone and new subperiosteal and subepiphyseal bone than in cortical bone in which the organic component is less. In other words, an exchange of atoms is constantly occurring in normal bone at a rapid rate without particular reference to osteoclasts *per se*, and without perceptible changes in the bone and blood com-

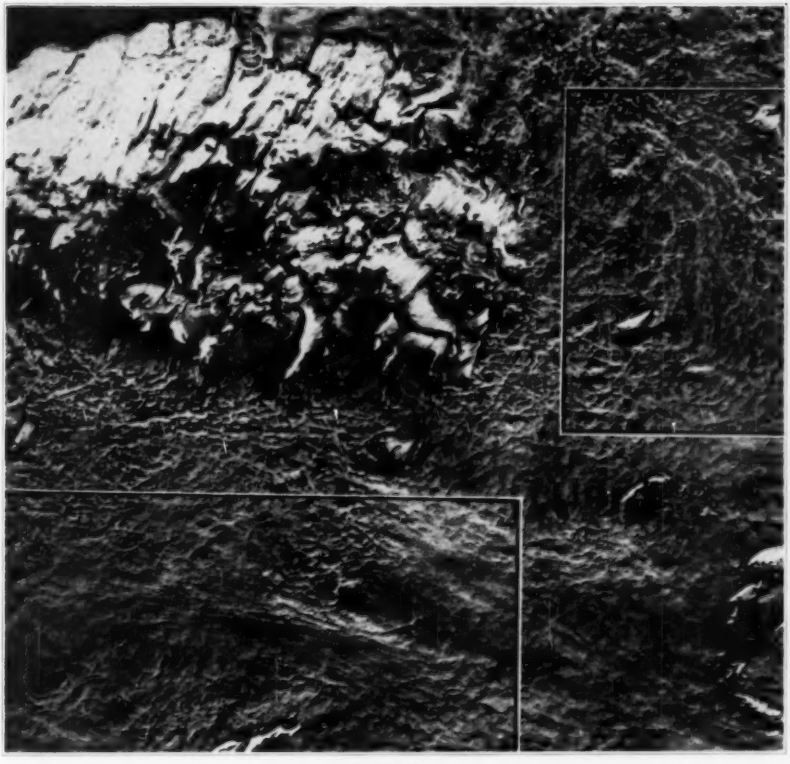


E. M. 27

E. M. 28

E. M. 27: *Cortex of tibia of cat, autoclaved ten minutes at twenty-seven pounds of pressure and blended* (Magnification 34,500 ×): The cement substance was largely removed. The collagen fiber was swollen, but many crystals were seen clinging to it.

E.M. 28: *Bone obtained from clavicle of a human, two days old, stained* (Magnification 34,500 ×): The bone crystals and their enveloping cement substance were stripped away easily from the collagen fiber on light blending (three minutes). The periodic pattern of cross striations was at approximately 640 Angström units with interspersed incomplete bands.



E. M. 29

Polished and etched rabbit femur (Magnification 9,500 ×): (1 millimeter = 1,053 Angström units). Courtesy of C. H. Gerould.

The electron micrograph is that of a shadow-cast replica of the polished and etched surface of the cortical bone of a rabbit femur. "The replica surface was parallel to external surface of the femoral shaft and about one-half millimeter below. Many areas of periodic structure are present, two of which have been marked. Periodicity, 665 Angström units" [44].

These areas of periodicity were interpreted as the site of collagen fibers which at this level of organization seemed to form a three-dimensional web. The one larger and several smaller projections in the field were interpreted as areas in which the replica material was impressed respectively into a lacuna and several canaliculi. From studies of such specimens it would appear that at this level of organization the collagen fibers do not travel in any predominant direction; and that at periodic intervals along the fibers the etching solution was less effective in removing the attached crystals. In this electron micrograph, which is comparable to a very small section of bone, no predominant direction of the collagen-fiber axis in relation to the long axis of the whole bone could be determined. Since this article was written, investigations by Rutishauser [103,104] have come to the author's attention, in which this arrangement of the collagen fibers in relation to a Haversian unit of bone has been studied by the use of replica technique and electron microscopy.

position if the intake and output of the necessary inorganic elements is balanced [112].

The inorganic bone crystals are exceedingly small and have a measured surface area of about 80 to 100 square meters per gram. Neuman [94] made this comment on these surface measurements: "At present it is not possible to state exactly what these surfaces mean in terms of physiological function. Certainly they serve to emphasize the dynamic nature of the calcified structure. Bone cannot be considered to be a stable system in which the inorganic phase is inert. The tissue fluids are literally flowing over acres of actively exchanging inorganic surfaces. It is not surprising that the calcium component of blood serum varies only slightly."

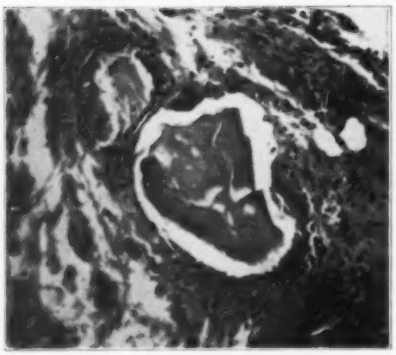


FIG. 4

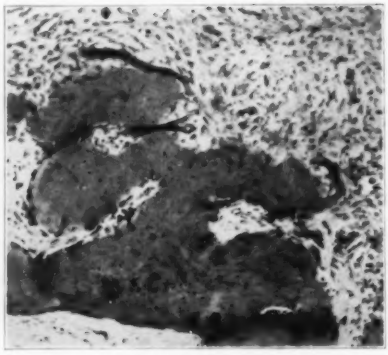


FIG. 5

Fig. 4: *Autogenous dog bone, autoclaved for four hours and transplanted to the anterior rectus sheath of the donor animal four weeks after transplantation* (500 ×, hematoxylin and eosin stain): Fibroblastic proliferation around this autoclaved bone was seen. Multinucleated giant cells were also observed. There was no evidence of osteoblastic proliferation. Electron micrograph of this autoclaved bone was similar to that shown in E. M. 3.

Fig. 5: *Autogenous bone graft which had been transplanted to the rectus sheath of a dog* (500 ×, hematoxylin and eosin stain): The photomicrograph showed the new-bone proliferation about an autogenous bone transplant to the anterior rectus sheath of a dog. Just below the surface of the transplant the lacunae were empty; but about the periphery of this transplant, new-bone trabeculae with a surrounding layer of osteoblasts were seen. The contrast between the osteogenic reaction to this fresh bone and the non-osteogenic reaction to bone from which the organic matter has been largely removed (Fig. 4) is obvious.

The cement substance of bone is conceived to act as the transfer agent between the crystals on one hand and the extracellular perivascular fluid on the other hand. The crystals then represent a storehouse of calcium and phosphorus atoms, the mass and exchange rate of which is controlled by the physical state of the organic matrix.

Work by McLean and Bloom [15, 85, 86, 87] gives evidence that the matrix which an osteoblast produces and controls can also be altered or catabolized by that cell when under proper stimulus. This may occur with the stimulus of excess parathormone [54].

Parallel to the matrix change, it is known that bone will give up its calcium in the presence of excess circulating parathormone even in the absence of renal function [2]. In hyperparathyroidism the rate of calcium turnover in bone and the rate of renal calcium excretion are both increased. This usually results in a total deficit, but at least in dogs the cystic bone changes associated with such a deficit can be lessened by an increased calcium intake [24].

In hypoparathyroidism the bone cell does not seem to be adequately controlled and it fails to metabolize its matrix in relation to the whole animal. Despite the needs of the total organism, the calcium is locked in the bone in hypoparathyroidism. The matrix is similarly out of control in avascular necrosis in which local hoarding of inorganic crystals occurs for lack of control of matrix.

Somewhere between these two extremes of excess parathormone and lack of parathormone exists a state in which the osteocyte under a normal parathyroid stimulus controls the matrix. The normally rapid transfer of atoms between the bone crystals and the blood would seem to depend on a matrix which is effectively governed by an osteocyte under proper hormonal control, particularly under parathyroid control.

Hyaluronidase apparently causes a swelling of the interfibrillar cement substance (E. M. 11 and E. M. 12). Under the influence of this enzyme fresh rib cortex appeared as shown in Electron Micrograph 24. It is noted that the crystals and the cement substance immediately about the collagen fibers do not seem to be affected by the enzyme, at least the crystals in this layer do not readily separate from the fibers.

A short period of autoclaving or boiling causes the collagen fibers to swell, and the interfibrillar cement substance to disappear. In Electron Micrograph 27 one sees such a swollen fiber with adherent crystals.

The crystals in the immediate vicinity of the fibers are arranged about the fibers so that the long axes of the crystals and the fiber are parallel. In some areas the crystals immediately next to the fiber are seen and these appear to be applied at regularly recurring intervals. The distance between these intervals is the same as that observed when collagen fibers are stained with phosphotungstic acid: approximately 640 Angström units. (E. M. 25). This is seen even more clearly in Electron Micrograph 26 which shows a crystal-encrusted bone fiber prepared in the presence of streptococcal hyaluronidase. This fiber is not stained and the periodic striations are made by the regularly spaced bands of crystals proximal to the fiber. The long axes of the crystals appear to parallel exactly, or within 45 degrees of, the long axis of the fiber (Fig. 1-E). Using the blending method of bone-sample preparation it was possible to detect only parallel orientation of the inorganic crystals and the collagen fibers in the crystal layers most adjacent to the fibers.

The orientation of the crystals in the immediate vicinity of the fibers and the fact that the crystals obviously lie in the cement substance leads one to assume that an orientation factor is at work. This factor may exert its effect on only those crystals in the immediate vicinity of the collagen fibers. It is thought that theoretically the polymers of mucopolysaccharides in the cement substance at the periphery of the collagen fibers are arranged in an orderly fashion, due to chemical bonds between these polymers and the collagen fibers. This orientation of the cement substance (in which the crystals form) may be reflected in the arrangement of the crystals immediately adjacent to the collagen fibers. An organic orientation might also account for the increased intensity of metachromatic staining of the cement substance in areas adjacent to the collagen fibers [35].

Discussion persists concerning the predominant direction of the collagen fibers in relation to the long axis of a bone. Ruth [102] states, "Osseous tissue is made up of fibrillae masked by a granular interfibrillar substance. Fibrillae are laid down in alternating lamellae of compactly arranged circumferential fibrillae with interfibrillar spaces small or absent, and diffusely arranged radial fibrillae with wide interfibrillar spaces. Fibrillae of the alternating bands bear an orthogonal relationship to each other, and lie in a transverse plane in relation to the long axis of a long bone. There are no longitudinal fibrillae." It should be noted that Ruth used Haversian units rather than bone with a purely circumferential lamellar pattern for his studies.

Collagen fibers seem to form a three-dimensional web throughout the bone at the level of electron-microscopic examination (E. M. 29). Mechanical forces [80] may play a part in determining the direction of fiber bundles and in affecting group arrangements of the inorganic crystals. However, on the basis of electron micrographs no definite interdependence of orientation of the *great bulk* of inorganic crystals and collagen fibers has as yet been demonstrated.

The possibility that the collagen fibers act as a nidus for crystallization of the matrix is suggested by the facts that collagen fibers appear before the crystals in the matrix of developing bone and that the most proximal crystals are regularly arranged about these fibers.

The collagen fibers in bone are fairly uniform in transverse measurement, between 500 and 1,200 Angström units according to our micrographs.

In the larger crystal masses which would appear to have developed in the interfibrillar spaces no suggestion of orientation of the crystals in relation to the collagen fibers could be observed. However, in these intact masses of crystals, the crystals had a definite laminated pattern (E.M. 19). This tendency to lie with their broader, flat surfaces opposing may well be a function of their shape in relation to the various mechanical forces under which they are placed. For instance, it is possible that a compression force acting on tabu-

lar crystals in a plastic matrix might cause the crystals to assume a laminated pattern (like bricks in a wall), so that the lamination planes would be tangential to the compression wave front [80]. The observed laminated arrangement of the bone crystals in such masses can probably be correlated with the observation [25,27,28,113] that there is a partial alignment of the *C* axis of the unit cells of the crystals in the long axis of long bones and radial axes of flat bones. This alignment of the *C* axis of the crystal unit cells was best observed in those bones having a purely circumferential lamellar pattern and not in those extensively replaced by Haversian units, such as the bat phalanx. Giganti [26] showed that this alignment tended to increase shortly after birth in the bones of certain animals.

Clark and Mrgudich [28] conclude that the effect of an attack of rickets on the cortex of the shaft of the long bones of a rat causes the inorganic crystalline material, although remaining chemically unchanged, to lose its preferred orientation which is normally in the long axis of the bone. The gross organic pattern of rachitic bone is disorganized in its enchondral stage of development. It is further distorted by compression forces, which due to its lack of inorganic crystalline support it cannot withstand [123]. Much bone replacement occurs as the rickets heal. As noted earlier, the *C*-axis "fibering" of bones is lost where there is marked Haversian replacement.

In infants, bone visibly bends under stress and returns to its original shape. This can be observed at the operating table. In bone, elasticity is afforded by the combination of the collagen fibers which can stretch many times their length without breaking [107] and the plastic, gel-like cement substance. Rigidity is afforded by the inorganic crystals. Weir, Bell, and Chambers [123] have shown that the elastic modulus of fresh bone is more like that of concrete or wood: bone can be bent almost up to its breaking point and yet return to its original shape. On the other hand, these investigators have demonstrated that bone has the strength of "mild" steel without its weight, for bone has a specific gravity of about 2, while "mild" steel has a specific gravity of 7.5. The efficiency of bone as a supporting structure combining elasticity with great strength depends on the relationship between its organic and inorganic components [77]. This combination occurs at a submicroscopic level which is at least partly visible in the electron microscope.

The observation that the crystals strip easily from the collagen fibers in very young and in senile bone during blending is of particular interest in the consideration of structure (E. M. 10, E. M. 21, and E. M. 28). The observation that the crystals lie in the cement substance can be related to statements by Weir, Bell, and Chambers [123] and Henschen [63] that the bone crystals must have to glide on one another when the bone bends. The activity of the individual and the use of the bone involve constant small, plastic deformations of bone. Henschen points out that when such gliding is not possible between the crystals, the elasticity of bone is lost. Avascular bone becomes brittle, and it breaks with continued use. This may be correlated with the tendency of avascular bone to fracture, for with the loss of blood supply the replacement and metabolic control of the cement substance by the osteocytes is stopped.

Bone considered roentgenographically in avascular necrosis shows two things: (1) A retention of the original x-ray density in the avascular portion. *Crystals in a matrix devoid of cellular control remain intact.* (2) Compressing and fracturing in the avascular portion occurs if the usual stresses are continuously applied to the affected portion while the avascular state exists. This compression and fracturing of necrosed bone becomes more marked with time and more apparent when the necrosed bone is partly removed and grossly weakened by "creeping substitution".

Adaptation of a bone involves not only changes in trabecular pattern and cortical thickness and shape, but also changes in the specific gravity and relative proportions of its organic and inorganic components [77]. Actually, these changes must all be made by cellular activity.

Since the bones do undergo small plastic deformations during use, it is not difficult

to see that with increased activity there are at least pressure changes exerted on the osteocytes. The stimulation of the hyaline cartilage covering the joint by forced increased activity has resulted not only in a slight increase in the number of cells but, more important, in an increase in the matrix about the cells [69]. If one may be allowed to suppose that similar stimulation of bone cells occurs with increased activity, this, in effect, would stimulate the cell to produce more of the basic materials for the development of more collagen fibers, more cement substance, and subsequently the deposition of more hydroxyapatite crystals in the cement substance. With such changes the bone would slowly adapt to increased activity by increased bulk. If the time necessary for the cells to make such changes in the matrix is not allowed as activity is increased, "fatigue" fractures occur. If the buffer of plastic cement substance between the crystals is not adequate for a series of back-and-forth excursions of crystal on crystal throughout the whole bone, the bending forces (for example, on a metatarsal during a forced march) will build up at a nodal point (for example, the neck of the metatarsal) and in time fatigue will occur at that point, causing a "fatigue" fracture,—in the case of the metatarsal, a "march" fracture [62].

From a mechanical standpoint, *the crystals* give bone rigidity by resisting compression forces. In their absence, as in rickets, the bone tends to deform. *The cement substance* appears to be a gel-like buffer between the crystals allowing small plastic deformations. The extent of motion of crystal on crystal would depend on the surface tensions between crystals and cement substance, the state of polymerization of the cement substance, its water content, and finally the relative amount of cement substance. Young bone with more organic matrix of a higher water content and a lower collagen content than that of old bone is more flexible and breaks in a typical greenstick fashion. The *collagen fibers* are conceived to act as tension members limiting the excursion of crystal on crystal. In view of the known elastic properties of these fibers, they would cause return of the bone to its original shape after small deformations. *Together* the collagen fibers and cement substance resist shearing forces.

Bone from the surgical point of view can act as a graft even after procurement methods that practically guarantee cell death (boiling, or homogenous transfer of cells with autogenous specificity). Fresh autogenous bone can, as a transplant, induce osteogenesis in the rectus sheath of dogs. Bone does not normally form at this site.

Autogenous fresh bone is most efficient as a graft or transplant. The factor of *tissue specificity* is thus circumvented.

From clinical experience the two general factors that increase the effectiveness of a bone graft or transplant are *porosity* or large surface area (cancellous bone as against cortical bone) which permits rapid invasion and resorption by host granulation tissue; and *high organic content* (embryonic bone, new callus, or cancellous bone as against cortical bone). Cancellous bone has both porosity and a relatively high organic content (Table I).

Urist pointed out [118] that the resorption of a bone graft starts the osteogenic mechanism. The fundamental process of graft resorption is the catabolism of the graft's matrix by the derivatives of the host's reticulum cells. The material may be poor in inorganic crystals and yet, if it is rich in typical bone matrix, it is apparently effective grafting material (os novum).

In this study, autogenous dog bone from which the organic matrix had been largely removed by four hours of autoclaving was used as a rectus sheath transplant. An electron micrograph of the material showed that the inorganic crystals remained, but by chemical analysis only 6 per cent. of the original matrix was left. The result of such a transplant is seen in Figure 4. As contrasted to a transplant of *fresh* bone placed in the opposite rectus sheath of the same dog (Fig. 5), the autoclaved transplant failed to show any osteogenesis. The cellular reaction to the autoclaved bone crystals was non-specific and consisted of simple fibrous encapsulation.

Bone contains a persuader of fibroblasts. This unknown factor is apparently resident in the organic matter of fresh bone and not particularly dependent on the existence of living cells. It certainly is not an attribute of the inorganic crystals.

SUMMARY

1. The inorganic crystalline component of bone occurs as crystals having average dimensions of 500 Angström units in length by 250 Angström units in width by 100 Angström units in thickness.

2. The crystals have a size range which they do not apparently exceed in normal bone. This range is from 1,500 Angström units in length to about 20 Angström units ±. The crystals are tabular in form, and in mature cortical bone some of the crystals have a regular hexagonal outline.

3. The crystals in newly formed and mature bone have the same general size and tabular form.

4. The crystals lie in the cement substance and not in the collagen fibers.

5. The pattern of atomic spatial arrangement characteristic of the hydroxyapatite crystal lattice may develop in matrices having considerable physical and chemical variation. Within this wide range of variation lies the physiological range of calcifying intrasomatic matrices. The fact that intrasomatic calcifications in general are hydroxyapatite is interpreted as follows: The hydroxyapatite crystal lattice is more stable under physiological conditions than alternate spatial arrangements of oxygen, hydrogen, calcium, and phosphorus atoms in other theoretically possible crystal lattices. At the periphery of a crystal lattice certain heterogenous substitutions may occur. This peripheral layer appears to be in contact with the cement substance of the bone matrix.

6. The collagen fibers in bone are fairly uniform in transverse measurement, between 500 and 1200 Angström units according to our micrographs. No visible difference is observed in these electron micrographs between these fibers and those of other connective tissues.

7. The collagen fibers in bone apparently swell on mild heating in water and the interfibrillar cement substance swells when it comes in contact with hyaluronidase.

8. Some of the crystals and cement substance closely ensheathe the collagen fibers. In the crystal layer most closely applied to the fiber the long axes of the crystals parallel the axis of the fibers and form a periodic pattern of rings around the fibers, the intervals between the rings being about 640 Angström units.

9. By the use of the blending method of bone-sample preparation, it was possible to detect this parallel orientation of the inorganic crystals and the collagen fibers only in those layers of crystals most adjacent to the fibers. In the interfibrillar spaces no such orientation could be definitely shown. However, in any group of crystals combining in large masses (in the interfibrillar spaces) they assumed a laminated structure. This tendency to lie with their broader, flat surfaces opposing may be a function of their tabular shape, and the added factor of packing is due to mechanical compression.

10. Calculations based on the dimensions of the inorganic crystals of bone observed in the electron microscope showed that:

A crystal 500 Angström units by 250 Angström units by 100 Angström units has (a) a surface area per gram of crystals of 106 m.^{2} and (b) the outer atomic layer in proportion to all atoms in the hydroxyapatite crystal was about 12 to 14 per cent.

A crystal 500 Angström units by 250 Angström units by 150 Angström units has (a) a surface area per gram of crystals of 84 m.^{2} and (b) an outer atomic layer in which the proportion to all atoms in the hydroxyapatite crystals was about 9 to 10 per cent.

On the basis of x-ray diffraction of samples used for electron micrography, it would appear that the inorganic crystals seen in the electron microscope are hydroxyapatite. The crystals were considered to be rectangular solids of tabular form with a specific

gravity of 3.0, a calcium-phosphorus ratio of 2.16, and unit cell dimensions of *A* axis = 9.47 Angström units and *C* axis = 6.88 Angström units, for the purpose of these calculations.

11. The calculations of size and surface area based on dimensions of the inorganic crystals of bone observed in the electron microscope correlate well with x-ray diffraction, gas adsorption, radio-active calcium and phosphorus exchange data, and the CO_3 "space" of bone presented by other investigators. This correlation of data lends full support to the author's conclusion that the crystals seen in these electron micrographs of bone are not artifacts of the preparation methods but pictures of the crystals as they occur *in vivo*.

12. The relationship of the inorganic crystals to the organic matrix is discussed. The structural characteristics of bone as skeletal material depend on this relationship. The site of crystal development and their size and shape appear to depend on this relationship. Others have shown that bone crystals form only in the matrix after the matrix has "matured" as shown by collagen fiber development. The theory is proposed that the collagen fibers may act as a nidus for crystal formation in the bone matrix.

Certain special staining characteristics and chemical analyses suggest that the cement substance of calcifying tissue is different from that in non-calcifying fibrous tissues. By electron micrographs it is shown that, although hydroxyapatite crystals may form in other normal or pathological tissues as well as in bone, the sizes or shapes of such crystals are often different from those found in bone. A special specificity of bone matrix as compared with other calcifying matrices is thus suggested by the characteristic size and shape of the crystals which it produces.

13. The cells as the organizing and sustaining members of the bone matrix play an essential role in this organic-inorganic relationship. It is suggested that, by slight alteration of the cement substance, thought to be due to cellular activity, the equilibrium between the calcium and phosphorus atoms of bone crystals, the calcium and phosphorus atoms of the cement substance, the calcium and phosphorus atoms of the extracellular fluid about the bone matrix, and finally the calcium and phosphorus atoms in the blood plasma, are controlled. The osteocytes responding to variations in the circulating hormone concentrations may thus alter the cement substance, making more or less calcium available to the other extracellular fluids from the bone crystals.

14. The inorganic crystals of bone observed in the electron microscope do not contribute osteogenic potency to a bone graft or bone transplant (outside of their function as a "honeycomb" that holds and possibly stabilizes the osteogenic material of the organic matrix of fresh bone).

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5. Electron Micrograph 3 is used with the permission of *Science* in which part of it was published on June 16, 1950.

6. Electron Micrograph 28 is used with the permission of the Dow Chemical Company. It was made by Dr. C. H. Gerould who used the technique described in References 42 and 43.

7. Tables III, IV, and V were constructed from material in the paper by Brandenburger and Schinz [19].

8. Table VI was taken from the work of Brandenburger and Schinz and is used with their kind permission.

9. Table VII: The samples listed in the table were prepared by the author. Nitrogen determinations were made in the laboratory of Dr. Herman Pearse, Professor of Surgery, University of Rochester School of Medicine and Dentistry. The data on the exchange of radio-active phosphorus were obtained by Dr. M. W. Neuman and Dr. W. F. Neuman of the University of Rochester Atomic Energy Project.

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DISCUSSION

DR. ROBERT W. JOHNSON, BALTIMORE, MARYLAND: Dr. Robinson has presented to us a major piece of basic research in our field of bone and joint surgery. In fact it is so basic that it really requires intensive study of the full text to appreciate it adequately. It is not the sort of paper that one can present so briefly, beautifully as he did it, unless it is to a small group of biophysicists or biochemists who have been working along similar lines and who can jump to the conclusions which he so readily reaches. We are not quite so agile, I fear.

Fortunately for me, Dr. Robinson supplied me well in advance with an adequately detailed and beautifully illustrated copy of his whole paper of some sixty pages with an additional bibliography of more than 100 articles. Thus I was able to study it carefully and to follow almost all of it, with a little outside help now and then. As a result of this, I gained a far clearer conception of the ultramicroscopic organization of bone than I ever had before. Not only has he demonstrated and measured the constituent crystals, but he has also related them to the chemical anatomy of bone as a whole. I was particularly struck by two of these observations of which he seems to be quite sure from his preparations.

1. That the inorganic calcium crystals (hydroxyapatite), which give bone its rigidity, are held in the "cement substance" and not in the collagen fibers of the matrix, though closely applied to them. I have had the impression that the collagen fiber itself was involved. A corollary to this is his belief that the collagen fiber of bone matrix seemed physically, at least, entirely similar to the collagen fiber of tendon or cartilage.

2. That there is an extraordinary amount of surface area provided by these minute hydroxyapatite crystals for the rapid exchange of ions by adsorption—86 square meters per gram of the crystals or approximately 40 square meters per gram of cortical bone. This is a rough calculation and is not so accurate as his. Thus, although bone appears to be so inaccessible and fixed to us who approach it mainly through surgery, it really is biochemically a "wide open space" and is a huge and accessible store house for readily mobilizable ions. Both the native calcium and phosphate of the basic crystals and the other magnesium, sodium, flourine citrate, and carbonate particles adsorb to their lattices. When we see the structure of the molecule, we can understand that there is considerable lattice work to which things can be adsorbed.

I have been thinking, in the past few years, especially in terms of the importance of the mucopolysaccharide in the biochemistry of calcification. This interest has been recently much stimulated by the observations of Duraiswami in the changes in foetal-cartilage formation in his work on the production of congenital deformities by the injection of insulin into the yolk sac, which suggested a disturbance of carbohydrate synthesis and the failure of proper mucopolysaccharide formation for collagen building at a critical period of development.

Perhaps Dr. Robinson in his future research can shed some light on this tremendously complicated problem of organic chemistry, too. His present work is a most fundamental and important contribution.

I want to express to Dr. Robinson my appreciation for his coming here as our guest and for presenting to us such a beautifully thorough and stimulating piece of basic research.

DR. JOSEPH S. BARR, BOSTON, MASSACHUSETTS: When the Chairman of the Program Committee asked me to discuss this paper, I hastened to decline the honor, assuring him that I was quite ignorant of the subject. He replied immediately, thanking me for accepting the assignment. This left me in a confused state, too weak to resist; so, here I am, painfully aware of my lack of experience in this field of study. However, my interest has been greatly stimulated; I have no doubt that I speak for all of us in extending to Dr. Robinson our thanks for bringing us this interesting and informative account of the appearance of bone as visualized with the aid of the electron microscope. Dr. Robinson has correlated micro-anatomy and histochemistry in an intellectually stimulating fashion.

His electron-microscopic findings have confirmed the evidence derived from x-ray diffraction studies, including that the inorganic component of bone has a crystalline structure (hydroxyapatite), and he has shown us photographic evidence of the size and shape of the crystals. The enormous surface area of the crystals (80–100 square meters per gram) is of fundamental importance in ion exchange between bone and body fluid. Living bone is, however, far from being a simple two-phase solid-liquid system; and, although the crystal size of living and dead bone is comparable, ionic exchange occurs twice as rapidly in living bone as in dead bone.

It therefore becomes necessary to study the organic components of bone and their anatomical and biochemical relationships to the crystalline inorganic components. At once we are confronted with the indisputable fact that the osteoblast, along with its variants, the osteocyte and the osteoclast, is an indispensible and primary factor. Differentiating within the primitive mesoderm it precedes, it appears to be the originator of the extracellular organic bone components, namely, collagen fibers and matrix (cement substance). The electron microscope visualizes not only the crystalline elements of bone but also the collagen fibers. Dr. Robinson's studies suggest that the hydroxyapatite crystals of bone align themselves about the collagen fibers in a periodic, orderly fashion. This may be the fundamental structural unit of the familiar trabecular pattern of bone. But much more verifying data must be accumulated before this hypothesis can be accepted. The technique of preparing bone specimens for electron microscopic examination using a Waring Blendor and then drying the suspended fragments in a vacuum, subjects the particles first to violent mechanical dispersal and then to the effects of surface tension in drying which may produce artifical distribution patterns not necessarily resembling living bone. The outstanding property of bone, its rigidity, is undoubtedly due to aggregates of hydroxy-calcium and phosphate crystals which are bound together in specific patterns by the cement substance. These crystals are the body's storehouse for calcium and phosphorus.

Although the collagen fibers of bone merit much more study than they have had, it is known that they contribute to the elastic property of bone and it is thought that they may be the framework upon which the deposition of crystals occurs.

The cement substance (amorphous matrix) is a highly complex mucopolysaccharide in the form of a viscous gel which acts as an exchange resin for the transfer of ions between the inorganic bone crystals and the extracellular perivascular fluid. The cement substance and the enzyme phosphatase present in it are both elaborated by the osteoblast. Also present in this amorphous matrix is a considerable percentage of the total sodium, carbonate, and magnesium found in the body.

The cement substance may have several functions, among them the stimulation of the deposition and regulation of the size of the bone crystals, the binding together of the crystals, and the regulation of the rate of calcium and phosphorus ion exchange between crystals and body fluid.

Of course the local factors which have so far been discussed are subject to innumerable generalized physical and chemical environmental influences, among which may be mentioned hormones, such as the parathyroid, vitamins D and C, thermal and mechanical variants, and circulatory and nutritional changes.

I think that it is fair to conclude that electron-microscopic studies of bone have made a modest contribution to our knowledge in this complex field, but the primary secret of bone growth still seems to lie hidden within the osteoblast, a part of that ultimate mystery—life itself.

DR. ROBINSON (closing): I wish to thank Dr. Johnson and Dr. Barr for their careful and kind exploration of this work and for their remarks. In regard to Dr. Johnson's criticism, I would like to say that it is our impression that the cement substance and not the collagen fibers is the important thing that differentiates the bone matrix from the matrices of other calcifying fibrous tissues. Studies with the electron microscope have shown that the crystals inside the bone matrix are afforded some protection in the presence of a strong acid by that cement substance and the individual crystals preserve their integrity within this extracellular space in the matrix.

In regard to the question about the grossness of the mechanical method used to break up the bone, let me say that it is a gross method, but, as a giant would have a hard time trying to catch a small mouse, so the blade in the blendor has a hard time hitting crystals. If the blade happens to miss the crystal, it misses it

(*Continued on page 476*)

PATELLAR GRAFT FOR SEVERELY DEPRESSED COMMINUTED FRACTURES OF THE LATERAL TIBIAL CONDYLE*

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The expanded upper end of the tibia is a cancellous structure with thin cortex. Consequently, since it overhangs the shaft on either side, it constitutes a point of weakness and of frequent fracture in adults. When the joint is forcefully struck from the lateral aspect, the strong tibial collateral ligament acts as a fulcrum, and the lateral femoral condyle is driven against the lateral articular surface of the tibia. The tibial collateral ligament may rupture, the lateral condyle may separate and be driven downward, or the lateral femoral condyle may be driven down into the upper end of the tibia with varying degrees of depression and comminution of the articular surface. In the first instance treatment usually presents no great problem. In the second, methods of treatment already in use are satisfactory; but, when comminution and depression occur to an appreciable degree, post-traumatic changes are probable and satisfactory reduction is occasionally impossible to obtain.

In most of these depressed comminuted fractures, the treatment of choice is by open reduction; the depressed surface is raised into position through a trap-door, cut just below the fracture, and the defect is packed tightly with bone chips to maintain reduction. In most cases a satisfactory knee results. The authors have in the past, however, had cases in which restoration of any kind of satisfactory articular surface was impossible. In these cases the meniscus may be found to be severely damaged and driven down into the tibial metaphysis. Upon trying to raise the fragmented condyle into position, the operator may find the bone too finely comminuted and just so much "sand".

Because the results in these severe cases were so poor, thought was given to devising a procedure by which a satisfactory joint might be obtained. Working independently and

FIG. 1-A

Case 2. September 19, 1949. Roentgenograms showed a severely comminuted and depressed fracture of the right knee.

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unknown to each other, the authors developed an operation the results of which have exceeded their hopes. One of the authors has done the operation five times, the other three. In all eight cases the results to date have been good. Five of these cases are reported. The three most recent cases have not been followed for a sufficiently long time to be presented. Although the authors realize that a report of five cases is not unquestionable proof of merit, they wish to point out that this procedure is reserved for those cases in which satisfactory reduction is otherwise impossible. This new procedure was first done five years ago.

FIG. 1-B

February 25, 1950. The patella has been used to replace the articular surface of the tibial condyle.

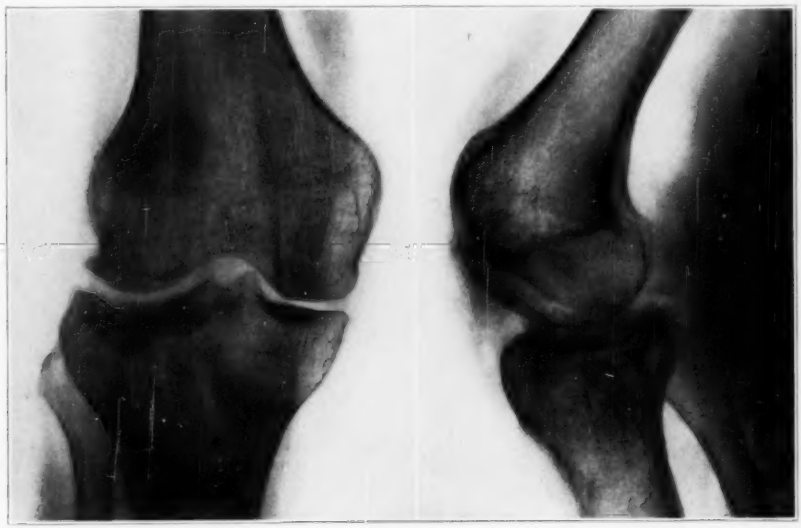

FIG. 1-C

September 28, 1951. End result.

CASE 1. A Negro bellboy was struck by an automobile, the bumper of which hit the lateral aspect of his left knee. Roentgenograms, made immediately after the accident, revealed a depression fracture of the lateral condyle of the left tibia. At open reduction the lateral articular surface was found to be shattered and the meniscus was found in shreds, driven down into the metaphysis. Restoration of a satisfactory articular surface was absolutely impossible. Examination of the patella revealed a normal articular surface.

In 1947, Moore, reporting his cartilaginous-cup arthroplasty for ununited fractures of the neck of the femur, conclusively demonstrated by means of microscopic slides of tissue which had been taken at autopsy from a patient who had undergone arthroplasty successfully nine years before that cartilaginous surfaces with underlying cancellous bone

FIG. 2-A

Case 3. November 23, 1949. Preoperative roentgenogram.

FIG. 2-B

November 28, 1949. Postoperative roentgenogram. Note that in this case the graft was fixed with two metal staples.

FIG. 2-C

November 20, 1951, two years and two months later.

can be successfully transplanted. In this report Dr. Moore summarized the history of transplanting hyaline cartilage. A study of the report [1] stimulated the development of the procedure here reported.

In Case 1 the thought arose that after patellectomy a satisfactory knee might be obtained by utilizing the articular surface of the patella to replace the destroyed surface of the

FIG. 3-A

FIG. 3-B

Fig. 3-A: Case 4. November 8, 1950. Roentgenograms showed a severely comminuted lateral and medial plateau fracture.

Fig. 3-B: November 13, 1950. The fractured lateral tibial condyle has been replaced by the patellar graft.

FIG. 3-C

September 19, 1951. End result, one year later.

lateral tibial condyle. Inasmuch as an unsatisfactory knee was certain to result from known methods of treatment the patella was removed and rongeured down to cancellous bone on its tendinous surface. The medial facet was removed and the lateral facet was set upon the end of the tibia to fill the defect and to replace the articular cartilage. Fixation was accomplished by means of an oblique metal screw. A long cast was applied to the limb for one month, after which time partial weight-bearing on crutches was allowed.

The patient at present has nearly ninety degrees of flexion and full extension. The joint has been entirely free of pain. Unfortunately the x-rays were lost and cannot be presented.

FIG. 4-A

January 19, 1951. Preoperative roentgenogram.

CASE 2. On September 19, 1949, a middle-aged woman was struck by an automobile; x-rays showed a severely comminuted and depressed fracture (Fig. 1-A). She was referred to the Miller Orthopaedic Clinic, Charlotte, North Carolina, where reduction was found to be impossible and the patella was transplanted to replace the articular surface (Fig. 1-B). No fixation of the graft was used.

The patient now has a painless knee with better than 50 degrees of flexion and full extension (Fig. 1-C).

CASE 3. On November 28, 1949, a woman, twenty-seven-years old, fell from a wagon and injured her left knee (Fig. 2-A). She was admitted to the James Walker Memorial Hospital, Wilmington, North Carolina. An open reduction was impossible because of the comminution. The patella was substituted and good smooth motion was attained. No cast was applied. The graft was fixed with two metal staples (Fig. 2-B). After two weeks partial weight-bearing on crutches was begun and the patient was discharged from the hospital.

Three weeks later the patient reported back, walking without pain or limp, having discarded her crutches without permission. At present she has 90 degrees of flexion, normal extension, and dances quite well.

CASE 4. A man, fifty-six years old, fell downstairs, sustaining a very severely comminuted lateral and medial plateau fracture (Fig. 3-A). At operation the medial condyle was found to be intact. The fractured lateral condyle was replaced by the patella (Fig. 3-B).

One year later he had full range of motion and no pain or swelling (Fig. 3-C). His only complaint is quadriceps weakness which occurred in spite of the physical therapy prescribed from the first day. Neither fixation nor immobilization was required.

CASE 5. A woman, aged sixty years, was seen three weeks after her fracture (Fig. 4-A). Again a patellar

FIG. 4-B

February 14, 1951. Postoperative roentgenogram.

FIG. 4-C

June 18, 1951. Follow-up roentgenogram made four months later.

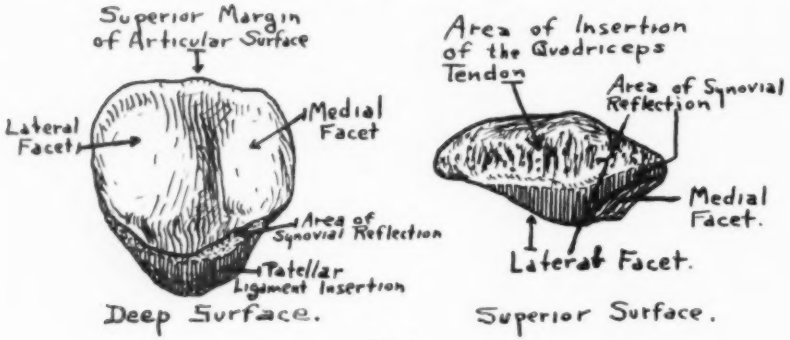

FIG. 5

Drawing of the deep surface and of the superior surface of the patella.

transplant was done (Fig. 4-B) and eleven months from the time of surgery the knee had 90 degrees of flexion and full extension. She was in a cast one month and started graded exercises in five weeks. Quadriceps exercises were stressed.

These five cases, one fixed with a screw, one fixed with staples, and three without fixation, seem to show that the basic principles of the procedure are sound regardless of any variation in technique.

The patella is a sesamoid bone, the largest sesamoid bone in the body. It is completely devoid of periosteum. The entire superficial surface is one of Sharpey fiber insertion and must be rongeured back to cancellous bone. In Figure 5 the articular surface is shown. There is the narrow medial facet and the broad lateral facet; the medial facet is worthless and should be removed.

In performing the operation either an anterolateral approach or an incision similar to Krida's may be used. The patella is turned upside down and removed by sharp dissection. It is then prepared in the manner previously described and is placed in the defect with the leg held in strong abduction; lateral stability is well restored at once. It is our experience that fixation of the graft is neither necessary nor desirable.

Experience with these patients has shown that stability of the joint is obtained immediately after the insertion of the patellar graft into the defect. No immobilization is required. The extremity is wrapped with an elastic bandage which extends from the toes to well above the knee. Gentle flexion of the knee, to about 10 degrees, is begun on the day following the procedure and is done several times a day. There has been no instance of a displacement of the patellar graft. At two weeks after the operation, the patient is allowed ambulation with crutches; weight-bearing is begun at six weeks. Shortly thereafter crutches may be discarded. We feel that weight-bearing stimulates the healing process.

In these eight cases we have noted no evidence of aseptic necrosis either in the patellar graft or in the compressed bony area beneath it. John Royal Moore has shown that cartilage with some cancellous bone attached to it does survive and does remain functional in hip reconstructions. The function of these knees in different age groups is certainly better than we have obtained with other methods. In our eight cases no major ligamentous tears were encountered. Certainly repair of such tears would add to the surgery and the ultimate prognosis in function, but we do not feel it would make a difference in the union of the patellar graft.

While this procedure should never become routine, we intend to continue to use this method in severely depressed comminuted fractures of the lateral tibial condyle. It is in the hope that it may be as gratifying to others as it has become to us that we offer this preliminary report.

1. MOORE, J. R.: Cartilaginous-Cup Arthroplasty in Ununited Fractures of the Neck of the Femur. J. Bone and Joint Surg., **30-A**: 313-330, Apr. 1948.

OSTEOGENETIC POTENCY AND NEW-BONE FORMATION BY INDUCTION IN TRANSPLANTS TO THE ANTERIOR CHAMBER OF THE EYE *†**

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New bone has been produced in tissue cultures [15, 42, 51], grown from transplants [9, 16, 21, 28], and described in pathological conditions of almost every organ in the body [2, 29]. The nature of the osteogenetic principle which initiates and sustains the process of new-bone formation is a fundamental problem of osteogenesis.

Beginning with the work of Barth in 1893, numerous histological observations have been reported in the literature to suggest, in some form, the hypothesis that new-bone formation is activated by those osteogenetic principles by which undifferentiated connective-tissue cells are transformed into bone cells. The experiments presented in this paper demonstrate the osteogenetic activity of 250 samples of various kinds of musculoskeletal tissues transferred to the anterior chamber of the eye. The eye facilitated continuous observation and recovery of the transplant, and excluded any direct contact with the skeleton of the host. Under such conditions *osteogenetic potency*—the capacity of the tissue to produce new bone—was exhibited by certain cells in the periosteum, cancellous bone, and bone-marrow reticulum which survived autogenous transplantation. This potency becomes manifest as *osteogenetic activity*, expressed as actual formation of bone by survival and proliferation of transplanted cells. When, on the other hand, the ingrowing cells of the host—in this case in the eye—are *induced* to form bone by contact with the substance of a transplanted tissue as described below, the process is that of *induction*. The process of induction elicits a potency in the ingrowing connective-tissue cells which otherwise might have remained latent. The nature of the induction process and the mechanisms, both physical and chemical, which may be involved have been developed in the field of experimental embryology and have been reviewed in detail by Weiss [62, 63, 64].

MATERIALS AND METHODS

White rats of the Wistar, Sprague-Dawley or a mixed Wistar-Sprague-Dawley strain were used in all the experiments. The specimens of the various tissues to be transferred were excised under open-drop ether anaesthesia and were drawn aseptically into the barrel of a blunt 16-gauge needle. The superior portion of the margin of the cornea was incised with a No. 11 blade. The needle was inserted into the incision and the specimen was ejected with a tight-fitting polished stylet. The details of each experiment will be described with the results.

The eye was removed at some interval between the sixth and thirty-sixth post-operative day, and fixed in a 10 per cent. solution of neutral formalin. The posterior chamber was opened widely in order to hasten diffusion of the fixative into the

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† Read at the Annual Meeting of The American Academy of Orthopaedic Surgeons, Chicago, Illinois, January 30, 1951. Revised manuscript received for publication November 14, 1951.

** The tables and illustrations in this paper were published in a preliminary report in the Transactions of the Third Conference on Metabolic Interrelations in New York, N. Y., on January 8, 1951, and are republished here with the permission of the Josiah Macy, Jr. Foundation.

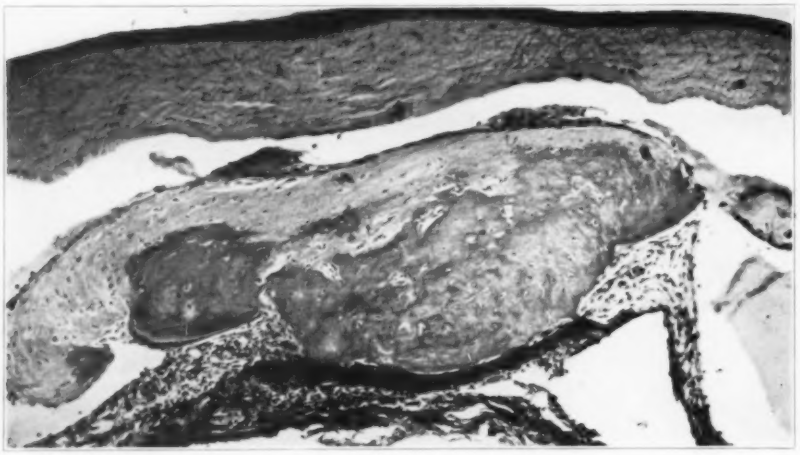

FIG. 1

Photomicrograph (× 120) showing new compact-bone formation five weeks after autogenous transfer of periosteum from the tibia of a three-week-old rat. (The cornea is shown at the top in this and all of the photomicrographs to follow.)

transplant. The eyes were examined roentgenographically and by gross dissection, and histological sections were prepared by methods described in a previous paper.[58]

EXPERIMENTS AND RESULTS

Autogenous Transplants of Periosteum

Experimental Procedure: The periosteum was removed surgically from the mid-shaft of the tibia in eight immature rats three weeks of age, and in eight adult rats approximately

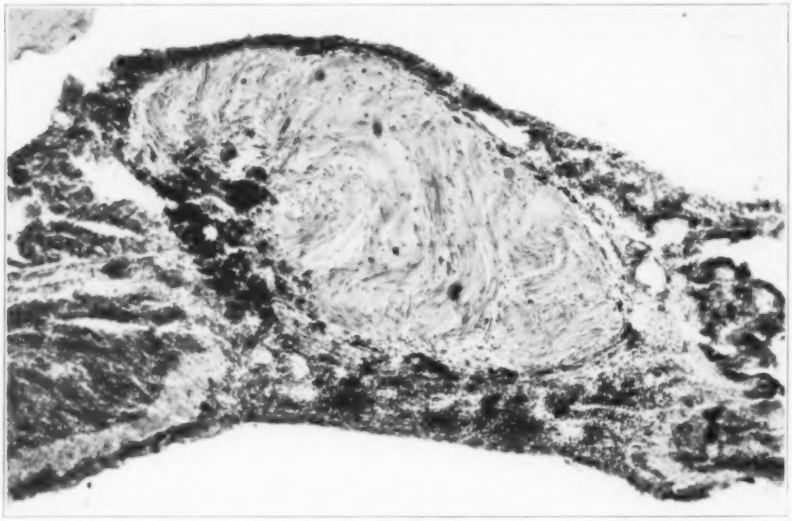

FIG. 2-A

Photomicrograph (× 75) showing a fragment of muscle transferred from the belly of the gastrocnemius. There is no evidence of new-bone formation after thirty-five days in the anterior chamber of the eye. Note the inflammatory, proliferative connective-tissue reaction of the host which encapsulates the muscle tissue and contains masses of old fibrin and hemosiderin.

one year of age. The specimens were injected into the anterior chamber of the eye and observed over a period of fifteen to thirty days, after which the animals were sacrificed and the eyes were removed for examination.

Results: The periosteum of young, rapidly growing animals produced new bone in four, or half of the total number of transplants. The periosteum from the same number of adult animals did not produce new bone (Table I). During the first fifteen days, the positive transplants showed the intramembranous type of bone formation which is typical of periosteal osteogenesis. After a period of five weeks in the eye, the new bone was transformed into a solid and very dense mass of cortical bone (Fig. 1). There was no intermediary stage of chondrogenesis, no marrow cavity, or any hematopoietic marrow at the conclusion of the growth of the transplant. The characteristic end product in the anterior chamber of the eye indicates that the periosteum contains cells with osteogenetic potency, and that this potency is specific for the formation of compact osseous tissue, without the concomitant production of cartilage or of hematopoietic marrow.

FIG. 2-B

Photomicrograph (× 70) showing a fragment of the capsule of the knee joint in the angle of the anterior chamber of the eye between the iris (shown below) and the cornea (shown above). There is no evidence of new-bone formation after thirty-five days in the eye.

Autogenous Transplants of Adult Periosteum Following a Fracture

Experimental Procedure: Closed fractures were produced in the right tibiae of immature rats by manual osteoclasis simply by bending the leg between the finger tips. In mature rats the osteoclasis was performed under light ether anaesthesia by bending the tibiae over the thin rolled edge of a metal cage. The fractures were exposed by open operation between one and four days after the injury. Until the third day, the periosteum was oedematous and detached from the cortical ends. Hence it was relatively easy to excise a specimen for transfer to the anterior chamber of the eye. On the fourth day, the periosteum was re-attached and usually contained a layer of typical osteoblasts.

Results: Periosteum from a mature rat produced new bone when transplanted as early as twenty-four hours after fracture, although similar grafts taken from the uninjured normal adult bone showed no osteogenetic activity (Table I). One-fourth of the transplants were positive for bone at forty-eight hours, and one-half were positive at seventy-two hours. The transfers made ninety-six hours after the fracture had cancellous bone in the

TABLE I

PERIOSTEUM

	Number of Transplants	Number Showing New Bone
Normal mature rat	8	0
Normal immature rat	8	4
Mature rat after a fracture:		
24 Hours	5	1
48 Hours	8	2
72 Hours	8	4
96 Hours	2	2

transplanted tissue, and showed that subperiosteal new-bone formation had already begun around the fracture. None of the one-day or two-day transfers showed that any bone tissue had been present in the sample previous to the transplantation.

Autogenous Transplants of Muscle, Fascia, Tendon, and Capsular Ligament

Negative results were observed in every instance thirty days after twenty-four samples of the following tissues had been transferred to the anterior chamber of the eye: normal muscle, fascia, muscle with fascia, joint capsule, tendon from immature animals, and tendon from mature animals. Two samples of hemorrhagic muscle excised from fracture sites twenty-four hours after the injury did not produce new bone. Two samples of autogenous urinary-bladder epithelium and two samples of ureter were also transplanted to the anterior chamber with negative results (Table II). There was no evidence of any absorption of the donor tissue (Figs. 2-A to 2-C).

Autogenous Bone Marrow

Experimental Procedure: Samples of bone marrow were removed from the center

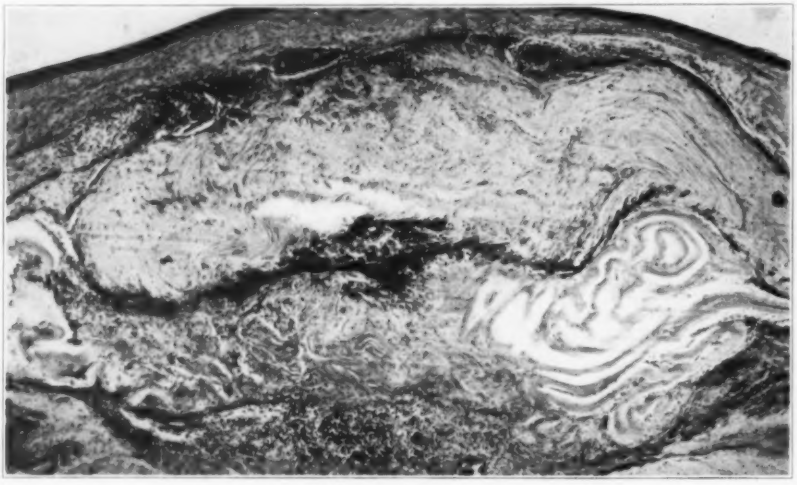

FIG. 2-C

Photomicrograph (× 70) showing a fragment of the Achilles tendon thirty-five days after transfer to the anterior chamber of the eye. The tissue is enveloped in granulation tissue containing lakes of old fibrin and hemosiderin, but there is no new bone.

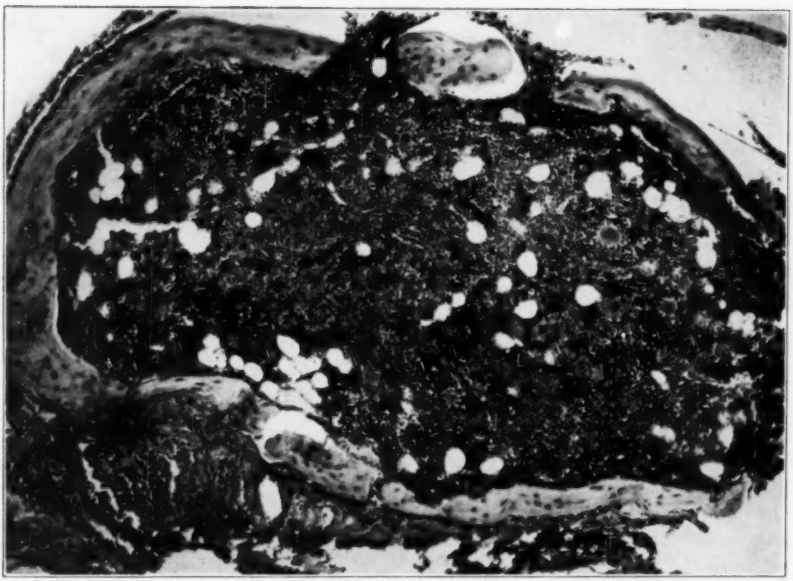

FIG. 3

Photomicrograph (× 110) showing the end product of a fragment of bone marrow after thirty days in the anterior chamber of the eye. A complete new sphere-shaped ossicle has formed. It contains active hematopoietic bone marrow and a wall of compact bone.

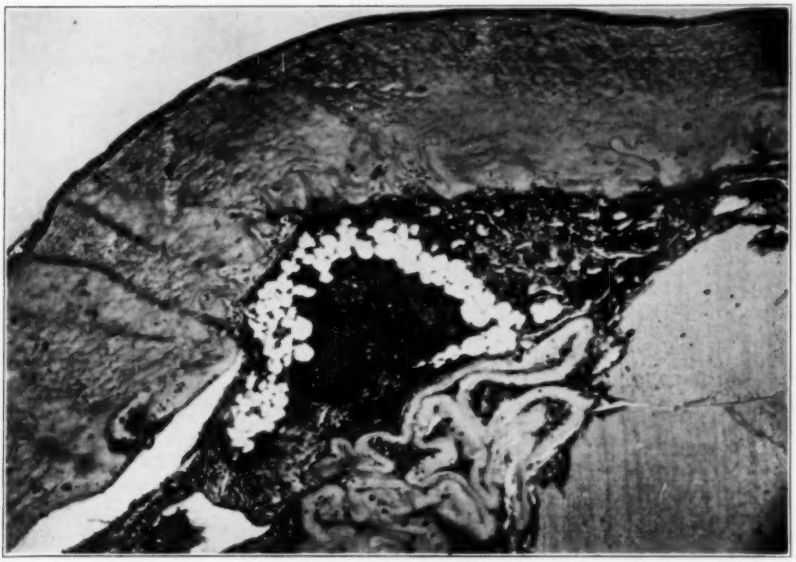

FIG. 4

Photomicrograph (× 90) showing a fragment of fracture hematoma after thirty-six days in the anterior chamber of the eye. The mass of old fibrin is surrounded by fatty fibrous connective tissue, but there is no new-bone formation.

TABLE II

AUTOGENOUS TRANSFERS OF MISCELLANEOUS NON-OSSEOUS TISSUE

	Number of Transplants	Number Showing New Bone
Normal muscle	10	0
Injured muscle after 48 hours	2	0
Muscle and fascia	2	0
Fascia	2	0
Tendo achillis	4	0
Joint capsule	2	0
Cartilage of the external ear	10	0
Semilunar cartilage, knee joint	10	0
Ureter	2	0
Urinary-bladder epithelium	2	0

of the primary marrow cavity of the tibiae with a teasing needle. Of the ten samples, seven were taken from normal adult tibiae, two from the proximal fragment of a healing tibial fracture twenty-four hours after fracture, and one from the proximal fragment of a healing tibial fracture forty-eight hours after fracture (Table III).

Results: At thirty days, two transplants of marrow from normal adult tibiae gave evidence of new-bone formation. The end product was considerably different in appearance, however, from that obtained from the periosteum. Marrow produced a complete new sphere-shaped ossicle with a primary marrow cavity and active hematopoietic bone marrow. Hence the cells from the bone marrow which survived and proliferated may be said to have had *organogenetic* as well as *histogenetic* potency (Fig. 3).

The Blood Clot in the Fracture Site

Seven specimens of the organizing hematoma were excised from fractures of the shaft of the tibia after one, two, three, four, and ten days of healing, and transferred to the anterior chamber of the eye. Thirty-six days later, there was no evidence of new-bone formation from any of these implants (Fig. 4).

Autogenous Transplants of Cancellous Bone

Eight successful transfers of cancellous bone from the proximal metaphysis of the tibia were examined on the eleventh, twenty-fifth, and thirty-fourth postoperative days (Table III). Appositional new-bone formation was observed at each interval in one or

TABLE III

AUTOGENOUS TRANSFERS OF BONE AND BONE MARROW

Tissue	Number of Transplants	Number of Days in the Eye	Number Showing New Bone
Bone marrow	5	30	2
Cancellous bone	2	11	1
Cancellous bone	2	25	1
Cancellous bone	4	34	4
Cortical bone *	10	28–32	2
Cortical fracture ends	2	28	1

* Periosteum marrow-free compact bone

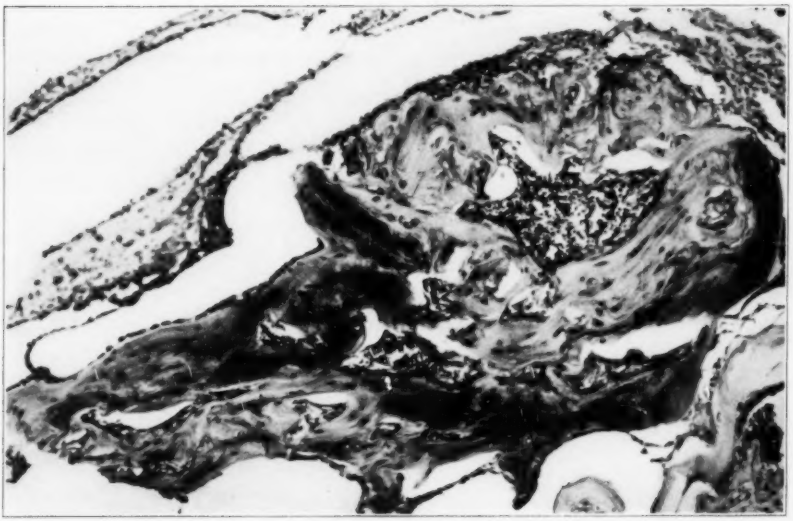

FIG. 5–A

Photomicrograph (× 135) showing a fragment of spongy bone from the upper end of the tibia after twenty-five days in the eye. Appositional new-bone formation occurs on the surfaces of the old bone tissue. Hematopoietic bone marrow appears in lakes between the new bone. There is a sharp, highly refractile line between the new bone which is deeply metachromatic-staining, and the old bone which is lighter staining and shows pyknotic nuclei or empty lacunae.

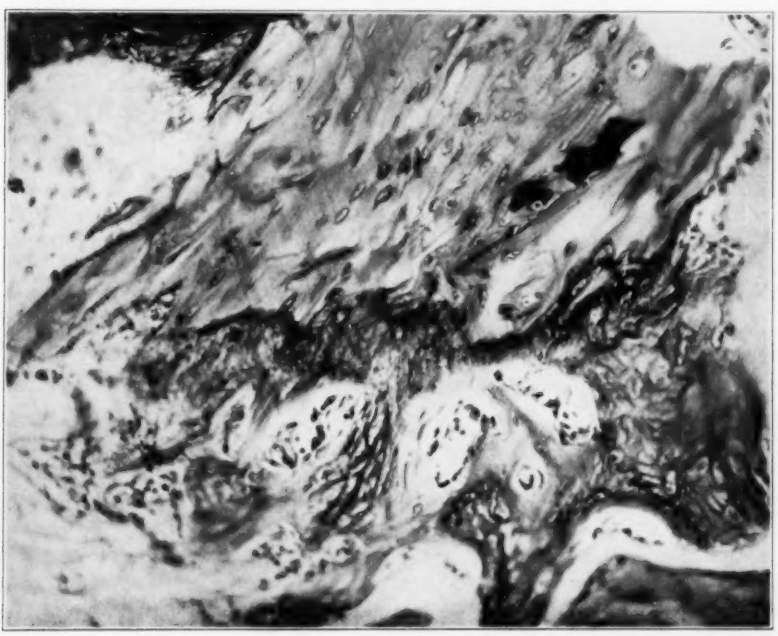

FIG. 5–B

Photomicrograph (× 250) showing a full-thickness fragment of cortical bone from the shaft of the tibia after twenty-eight days in the eye. There are empty lacunae in the old bone which stain poorly in the upper part of the section. The metachromatic-staining new bone is fibrous in structure, and is sharply demarcated in the lower half of the picture.

TABLE IV

AUTOGENOUS TRANSFERS OF FIBROCARTILAGINOUS CALLUS FROM HEALING FRACTURES, TEN TO TWELVE DAYS AFTER FRACTURE

Number of Successful Transfers	Number of Days in the Eye	Number Showing New Bone
1	6	0
3	7	0
3	8	0
2	9	0
5	10	3
5	11	4
1	13	1
3	17	2
1	18	1
1	23	1
1	27	1
1	30	1
7	35	7
2	36	2

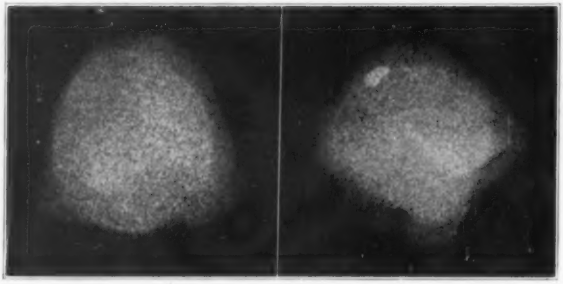

FIG. 6-A FIG. 6-B

Fig. 6-A: Roentgenogram of the eye containing the transplant of muscle shown in Fig. 2-A, shows no radiopaque material. Compare with Fig. 6-B.

Fig. 6-B: Roentgenogram of an eye thirty-five days after transfer of eleven-day-old fibrocartilaginous callus. Note the new ossicle formed in the angle of the anterior chamber. The eye was roentgenographically positive for calcification only when there was new-bone formation.

more of the specimens. The new bone appeared to be laid down on the necrotic bone trabeculae of the transplant as soon as a capsule of granulation tissue developed and ingrowth of blood vessels from the host was evident. The *absorption* of the old bone tissue was accompanied by a progressive increase in the volume of the new bone. After twenty-five days, new hematopoietic marrow developed in the interstices of the new bone tissue (Fig. 5-A). The end product of the transplant was also a complete new ossicle.

Autogenous Implants of Cortical Bone

Experimental Procedure: Twelve implants of cortical bone were transferred to the anterior chamber of the eye. Of these, two were bone ends of healing fractures forty-eight hours after fracture, and ten were of cortical bone freshly removed from normal uninjured tibiae.

Results: There were no positive results in less than twenty-eight days from transfers of compact bone devoid of periosteum or marrow, but a scant deposit of new bone appeared in two instances after the fourth week in the eye. Another sample which contained some cancellous bone on the medullary surface of one fragment showed vigorous bone formation. The new bone usually appeared where donor tissue had been eroded by ingrowth of new blood vessels and connective tissue. There was no new-bone formation from four technically perfect transfers of a thin acellular strip of compact bone. These were

encapsulated in fibrous connective tissue and had not been eroded or absorbed within a twenty-eight-day period in the eye. None of the marrow-free transfers, including the tissues which induced osteogenetic activity, appeared to contain cells which survived transplantation or produced an outgrowth (Fig. 5-B).

Autogenous Transfers of Fibrocartilaginous Callus

Experimental Procedure: Thirty-six transfers of autogenous fibrocartilaginous callus

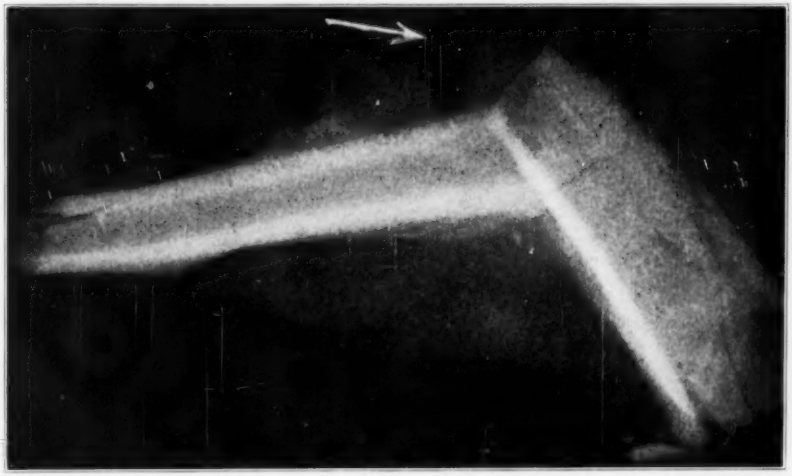

FIG. 7–A

Roentgenogram (× 5.5) showing a fracture of the mid-shaft of the tibia which was split in half longitudinally after eleven days of healing. The radiolucent area in the callus (see arrow) is the space from which a block of tissue was excised for transfer to the anterior chamber of the eye. The block of tissue was divided in half; one half was fixed for histological sections to determine its composition as shown in Fig. 7-C.

FIG. 7–B

Photomicrograph (× 8) showing the entire anterior portion of the callus of the fracture shown in Fig. 7-A. The histological composition of the excised area is shown in Fig. 7-C.

FIG. 7-C

Histological section of one half the tissue excised from the fracture callus shown in Figs. 7-A and 7-B. This is a typical sample of fibrocartilaginous callus, and contains actively growing spindle-shaped fibrous connective-tissue cells, fibrocartilage, and hyaline cartilage.

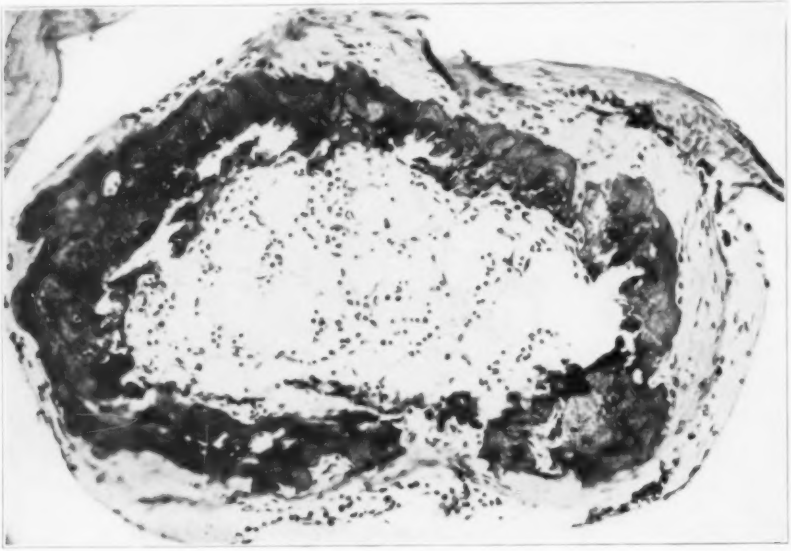

FIG. 7-D

Photomicrograph showing the end point of a transplant of one half of the excised area of callus shown in Figs. 7-A, 7-B, and 7-C after thirty-five days in the eye. This complete spherical ossicle which conformed to the anterior chamber of the eye is the end product of the transplant.

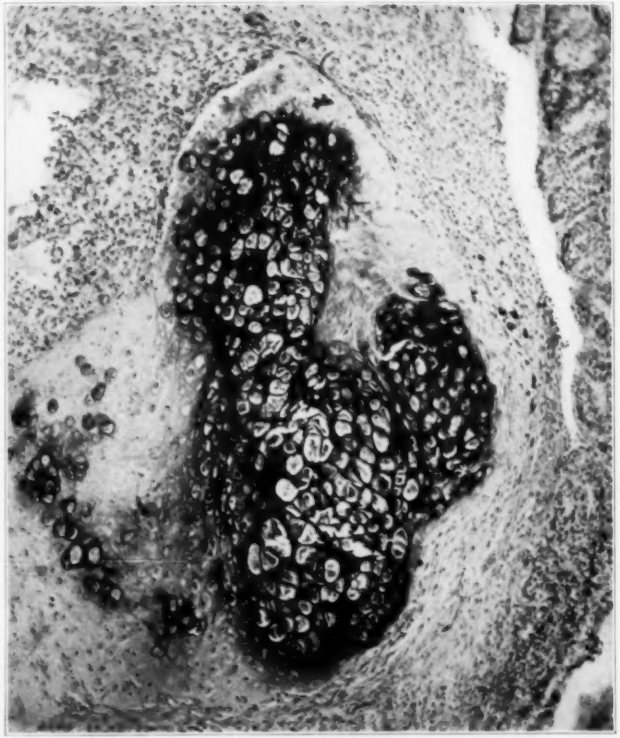

FIG. 8–A

Photomicrograph (× 135) showing a fragment of fibrocartilaginous callus encapsulated in granulation tissue after seven days in the eye. At this stage, there is a sharp line of demarcation between the tissues of the donor and the host. The surface of the transplant shows metachromatic staining, but there is as yet no ingrowth of new vessels or absorption of the transplant.

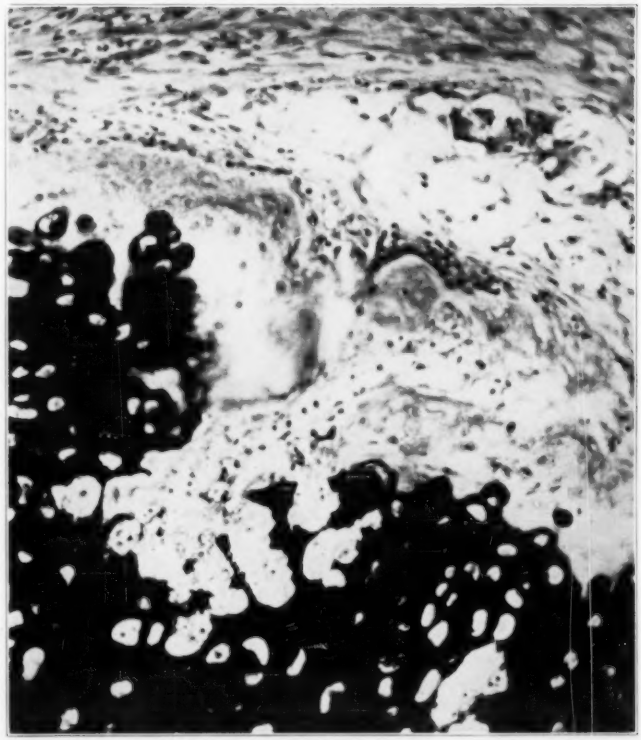

FIG. 8–B

Photomicrograph (× 270) from another transplant of fibrocartilaginous callus under high-power magnification, showing the earliest invasion of the donor tissue after eleven days in the eye. The beginning new-bone formation occurred with the first ingrowth of new blood vessels and in association with the absorption of the donor cells.

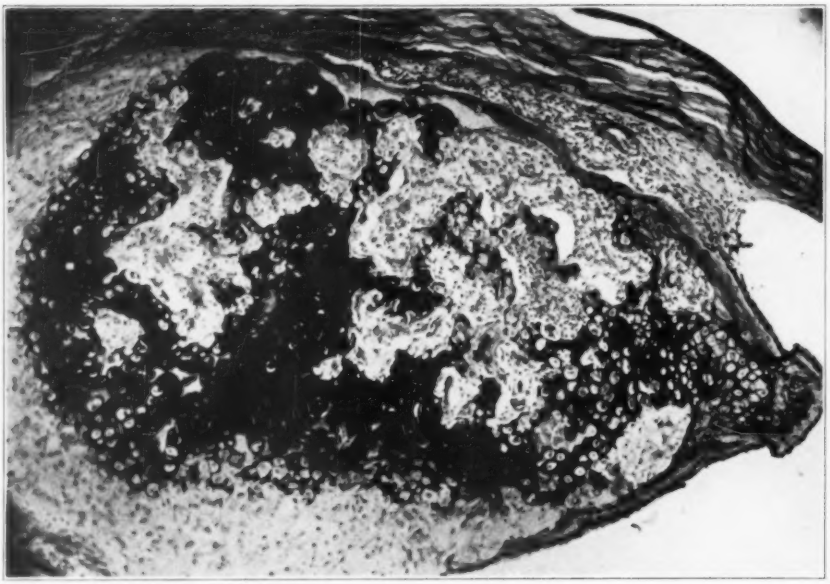

FIG. 8-C

Photomicrograph (× 100) of a transplant of fibrocartilaginous callus seventeen days after transfer to the anterior chamber of the eye, showing further absorption of cartilage and a thin wall of new-bone formation on the surface of the donor tissue.

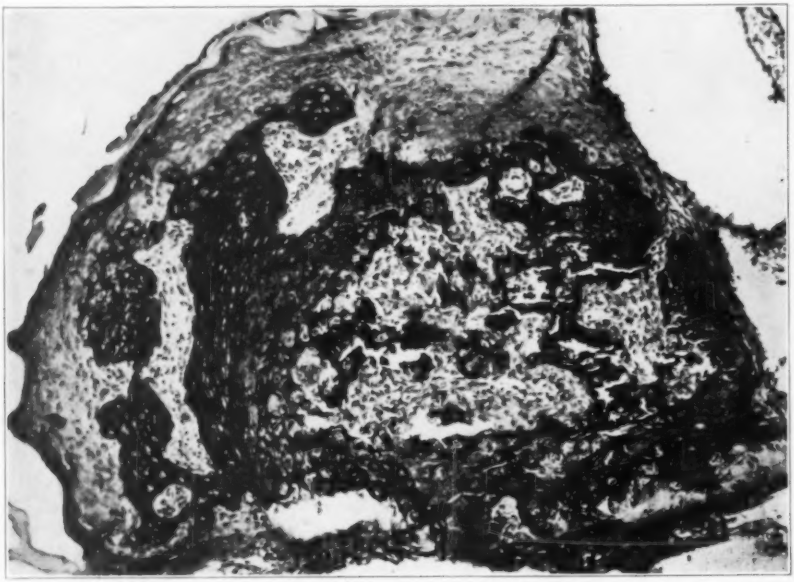

FIG. 8-D

Photomicrograph (× 135) of a transplant of fibrocartilaginous callus twenty-three days after transfer to the anterior chamber of the eye. Nearly all of the cartilage has been absorbed and replaced by a spherical mass of new spongy bone.

were examined at various intervals between six and thirty-six days after implantation in the rat's eye as shown in Table IV. Closed fractures of the tibia were made in adult rats by manual osteoclasis as previously described. The fractured leg was amputated under ether anaesthesia after ten to twelve days of healing. After the tibia had been dissected free of skin, the leg and fracture site were split longitudinally. A fragment of fibrocartilage was excised from the callus with a No. 11 blade under a dissecting microscope. Histological sections were made of the whole specimen of callus from which the fibrocartilaginous tissue was excised. The composition of the sample was ascertained in two ways,—one half of the sample was transferred to the eye, and the other half was prepared for histological sections. By these methods, it was possible to exclude any sample which might have contained bone tissue prior to transplantation.

FIG. 8–E

Photomicrograph (× 100) of the end product of a transplant of fibrocartilaginous callus twenty-seven days after transfer to the anterior chamber of the eye. Spongy bone similar to that shown in Fig. 8-D has now been reconstructed into a wall of compact bone. The result is a permanent complete ossicle filled with active bone marrow.

Results: Nine transplants examined between six and nine days after transfer showed no new bone in either roentgenograms or histological sections. Various stages of the process of new-bone formation were observed in twenty-three of twenty-seven other transplants examined between ten and thirty-six days after the transfer to the eye. The transplantation of these tissues consistently led to an extraordinarily high degree of osteogenetic activity. The histological changes by which such transplants were replaced by bone have not been previously described in the literature.

In the first week after transfer, the transplant usually became attached to the iris in the angle of the anterior chamber of the eye. The acute inflammatory reaction and process of implantation of the transplant appeared to be the same as that from a wide variety of grafts which have been described [11,19]. The mass of fibrocartilaginous tissue became encapsulated in inflammatory and granulation tissue which later developed into a highly vascular, slightly denser type of fibrous connective tissue.

During the second week in the anterior chamber of the eye, the capsule enclosing the transplant developed in two layers,—an outer layer of dense connective tissue and an inner layer of mesenchymal cells and vascular tissue.

FIG. 9-A

Photomicrograph (× 145) showing a fragment of fibrocartilaginous callus which had been devitalized by freezing in carbon dioxide before being transferred to the eye. After thirty-six days in the anterior chamber, a scant deposit of new bone was formed on the surface of the transplant.

The transplants of fibrocartilaginous callus contained two or three types of cells: spindle-shaped fibrous connective-tissue or mesenchymal cells; granulation tissue of the organized hematoma; and fibrocartilage and hyaline-cartilage cells which are probably differentiated from the similar mesenchymal cells growing in the fracture gap. Although it is possible that some of the undifferentiated fibrous connective-tissue cells possessed osteogenetic potencies and could have differentiated directly into osteoblasts and new bone, such a process was not observed. Actually, the new-bone formation began on the surface of the transplant in the space between the vascular layer of the capsule formed by the host and the metachromatic staining surface layer of cells of the donor tissue. It was difficult to determine precisely whether the osteoblasts were derived from the host or from the donor cells. It was evident, however, that the new bone first appeared on the surface of the absorbing transplant, and was derived from vascular buds from the inner wall of the host capsule. The ingrowing perivascular connective-tissue cells of the host appeared to be the source of the new bone cells. This process began as late as four to five weeks in experiments with transplants of periosteum marrow-free compact bone in which there were no viable cells demonstrable in the donor tissue. The activity of the cartilage cells of the callus will be described from observations upon transplants of epiphyseal or articular cartilage, which contained only the one kind of cell.

During the third week in the eye the transplant continued to be absorbed and new bone was rapidly laid down inside the transplant on the surface of the cartilage matrix. The appearance of the process was the same as in typical endochondral ossification anywhere in the skeleton. Some of the bone trabeculae showed persistent cores of cartilage matrix,

TABLE V

AUTOGENOUS TRANSFERS OF DEVITALIZED FIBROCARTILAGINOUS CALLUS

Treatment	Number of Transplants	Number of Days in the Eye	Number Showing New Bone
Frozen	3	36	1
Boiled	3	36	2

whereas in other places the cartilage matrix was bare and surrounded by osteoclasts, primitive marrow, and fibrous connective-tissue cells.

During the fourth week in the eye the new bone formed a complete ring around the absorbing transplant. The outer shell changed from spongy bone to cortical bone, while the cancellous bone continued to form in the inner parts by endochondral ossification. A primitive type of bone marrow, containing cords of hematopoietic cells, appeared between the new bone trabeculae.

During the fifth week in the eye the inner formations of cancellous-bone tissue were absorbed, and a single large space or primary marrow cavity was formed and filled with active hematopoietic marrow. The end result was the transformation of the donor tissue into an ossicle of mature cortical bone which conformed in general outline to the shape of the anterior chamber of the eye (Figs. 6-A and 6-B, 7-A to 7-D, and 8-A to 8-E).

Both the histological observation of the growth of new bone, in the presence of

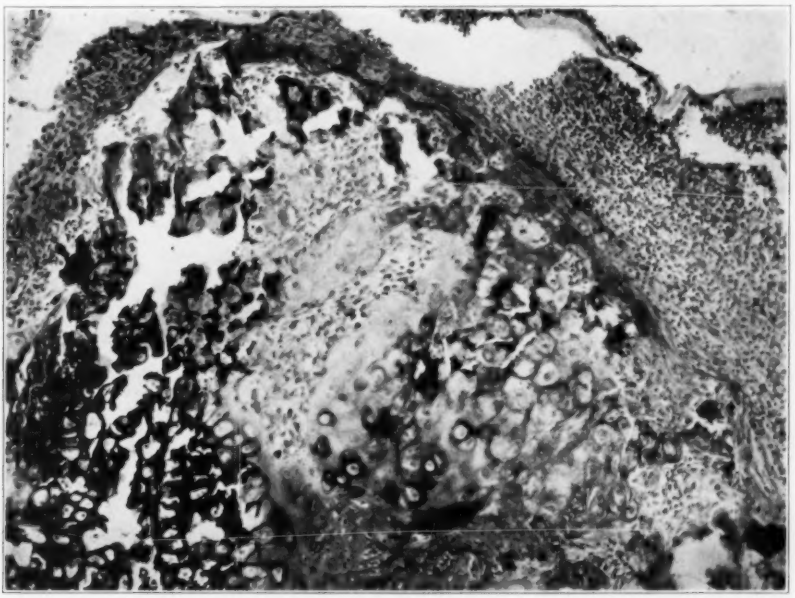

FIG. 9-B

Photomicrograph (× 145) showing a fragment of fibrocartilaginous callus which had been devitalized by boiling at 32 degrees centigrade for three minutes before being transferred to the anterior chamber of the eye. After thirty-six days in the eye, there was an ingrowth of blood vessels and primitive connective tissue, absorption of cartilage, and a thin layer of new-bone formation just beginning on the surface of the donor tissue similar to the process in the fresh viable transplants shown in Fig. 8-B.

TABLE VI

AUTOGENOUS AND HOMOGENOUS TRANSFERS OF EPIPHYSEAL CARTILAGE

Number of Transfers	Number of Days in the Eye	Number Showing New Bone
	AUTOGENOUS TRANSPLANTS	
2	11	0
2	13	2
2	16	2
4	18	4
1	21	1
2	31	2
2	34	2
1	35	1
2	36	2
	HOMOGENOUS TRANSFERS	
7	21	7

transplanted fibrocartilaginous callus, and the pattern of the ossicle, which is formed complete with hematopoietic marrow, suggest that the new bone was produced by organogenetic as well as histogenetic induction, although the possibility of survival and proliferation of some transplanted cells has not been excluded.

Devitalized Autogenous Fibrocartilaginous Callus

Experimental Procedure: Six specimens of fibrocartilaginous callus were obtained as described above and treated as follows: Three were boiled in normal saline solution and three were frozen with carbon dioxide gas for a period of three minutes. The specimens were placed in sterile saline solution at 32 degrees centigrade for three minutes and then transplanted to the anterior chamber of the eye. The end products of all of these transfers were examined on the thirty-sixth postoperative day (Table V).

Results: Three of the six transfers, two of the boiled and one of the frozen implants, produced new bone. The process differed from that observed in fresh implants only in the

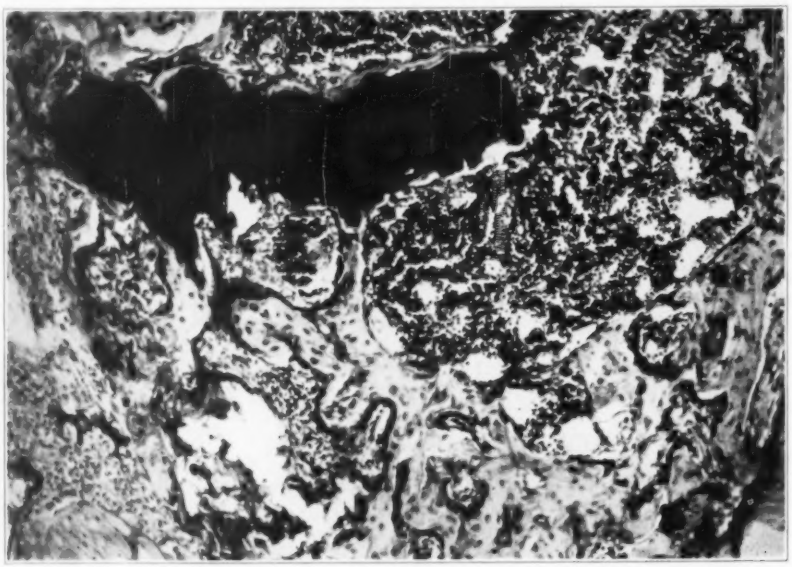

FIG. 10-A

Fig. 10-A: Photomicrograph (× 135) showing a fragment of fresh epiphyseal cartilage from the tibia of a four-week-old rat after eighteen days in the eye. Vigorous new-bone formation was produced similar to that obtained from fibrocartilaginous callus as shown in Fig. 8-D.

Fig. 10-B: Photomicrograph (× 105) showing the product of a similar transplant of epiphyseal cartilage after thirty-six days in the eye. The germinal cells of the cartilage persist on one side of the new ossicle which developed in the manner similar to that shown in Figs. 3, 7-A to 7-D, and 8-A to 8-E.

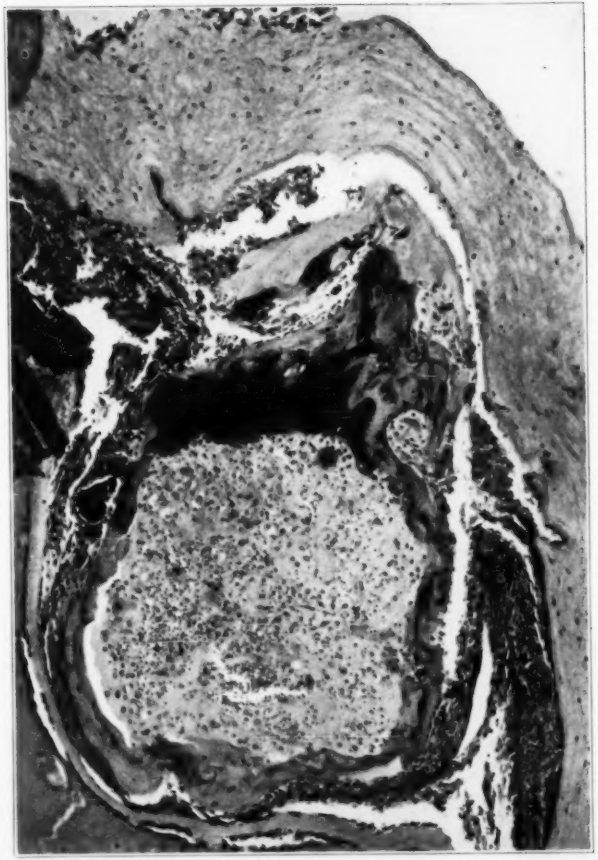

FIG. 10-B

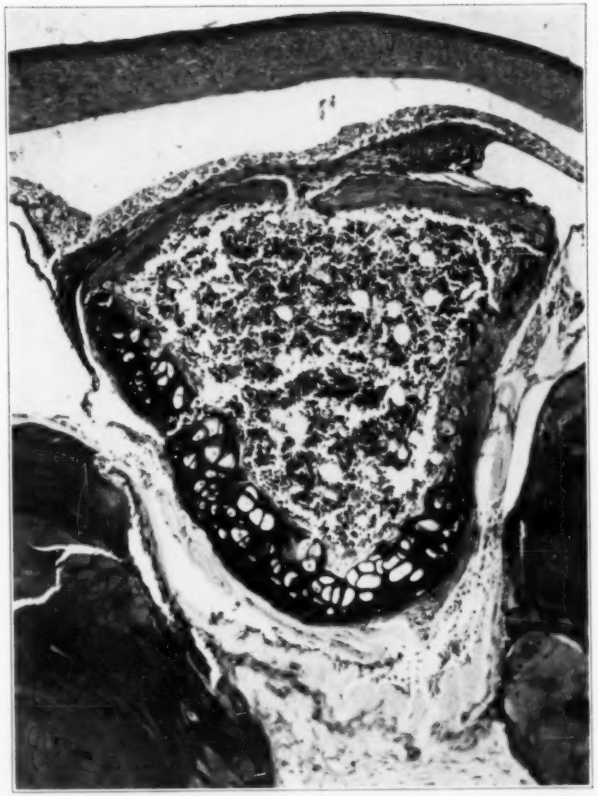

FIG. 11

Photomicrograph (× 105) showing the product of a transfer of articular cartilage from the upper end of the tibia of a two-week-old rat to the anterior chamber of the eye. A new ossicle complete with an articular surface and active hematopoietic marrow has formed within thirty-five days in the eye.

following respects: It was initiated at four to five weeks in the eye. Compared with fresh autogenous transplants, which produce new bone in less than two weeks, the devitalized transfers were enveloped in an extraordinarily thick capsule of fibrous tissue and showed limited deposits of new bone. By a process similar to that in viable transplants, however, the new bone developed from ingrowing perivascular connective tissue and was laid down first on the surface and then inside the substance of the devitalized transplant (Figs. 9-A and 9-B).

There was no difference in the activity between the frozen and the boiled transfers. The new bone was laid down around the stalks of numerous vascular buds from the fibrous capsule of the host which invaded and eroded the transplant. The pattern of absorption was variegated and independent of the pattern of the process of new-bone formation. The source of the new bone from dead transplants can be explained only as the result of induction.

TABLE VII

AUTOGENOUS TRANSFERS OF ARTICULAR CARTILAGE

Number of Transplants	Number of Days in the Eye	Number Showing New Bone
1	11	0
1	13	0
1	14	0
1	21	1
1	31	1
1	34	1
2	35	2
1	36	1

Autogenous Epiphyseal Cartilage

Experimental Procedure: In order to obtain a pure sample of cartilage cells, eighteen transplants of epiphyseal cartilage were excised from the center of the upper tibial epiphyseal cartilage of four-week-old rats with the aid of a dissecting microscope, and transplanted to the anterior chamber of the eye. The grafts were examined in between eleven and thirty-six days, as shown in Table VI.

Results: All of the transplants had produced new bone by the end of the second week. The new bone again appeared on the surface of the transplants inside the vascular layer of the capsule of fibrous connective tissue formed by the host. The sequence of events was the same as with the transplants from the fracture callus. The new bone developed in association with an ingrowth of blood vessels and absorption of the cartilage matrix. The end result was the formation of a complete spherical ossicle filled with hematopoietic marrow. Some of the transplants were found to contain the germinal or "row mother cells" of the original epiphyseal cartilage, and persisted even after the final stage of the osteogenetic reaction. The result was a mature ossicle complete with an epiphyseal cartilage. It was doubtful, however, that transplanted epiphyseal cartilage continued to proliferate and more likely that it only persisted after seven weeks in the eye.

There was no evidence of transformation of chondrocytes into osteoblasts or osteocytes. The hypertrophic vesiculated cartilage cells showed metachromatic staining, degenerative changes, and liberation of the cells from the lacunae. The process appeared to be the same as that of endochondral ossification anywhere in the skeleton (Figs. 10-A and 10-B). Osteogenesis appeared to have been initiated wholly by induction.

Homogenous Epiphyseal Cartilage

Experimental Procedure: With the technique described above, the activity of the cartilage cells was also investigated by the use of homogenous transplants, in which it might be assumed that the cells would have less vitality, enabling them perhaps to survive but not to proliferate.

Results: As shown in Table VI, seven transplants were examined at twenty-one days, and all gave evidence of new-bone formation. There was little if any difference in the activity of autogenous and homogenous transplants. Perhaps the amount of new bone in some instances was somewhat less at three weeks than of autogenous cartilage at two

weeks, but not at the conclusion of the osteogenetic reaction. Osteogenesis was initiated by induction.

Autogenous Articular Cartilage

Experimental Procedure: In shavings of the articular cartilage of young rats, it was technically possible to obtain a pure specimen of hyaline cartilage without osteoblasts. Nine such autogenous samples of the thick articular cartilage from the upper end of the tibia of two-week-old rats were successfully transferred to the anterior chamber of the eye (Table VII).

Results: New-bone formation was produced in the same way as with epiphyseal cartilage and all of the transfers showed new bone after three weeks. The germinal cells on the synovial side of the cartilage appeared to survive and resist absorption. The end product in a few instances was a whole new ossicle complete with an articular surface. The new bone appeared to be induced by the donor tissue (Fig. 11).

Autogenous Semilunar Cartilage

Experimental Procedure: Samples of a more highly specialized or differentiated type of fibrocartilage were obtained from the semilunar cartilage of the knee joint. Ten successful autogenous transfers were made following arthrotomies and were examined after five weeks in the eye.

Results: Two specimens showed old formations of bone in the original transplant, but the fibrocartilage was encapsulated and unchanged. Later, when a large number of rats' knee joints were examined, it was found that ossification of the semilunar cartilage is a special characteristic of the rat. There are normally two ossification centers present in each semilunar cartilage in the knee joint of the adult rat.

A similar experiment was therefore done with two young rabbits which do not have ossification centers in the semilunar cartilage, but neither did these transfers produce new-bone formation within thirty days.

Autogenous Ear Cartilage

Experimental Procedure: Samples of cartilage were obtained from the external ear of immature rats. This elastic cartilage, which does not ossify in the lifetime of the rat, is composed of large, clear cells with thick capsules, and contains very little matrix.

Results: Ten successful transplants of this highly cellular type of cartilage produced no bone formation after three to four weeks in the eye. The transplants were encapsulated in fibrous connective tissue and were neither penetrated by vessels nor absorbed during this period of time.

DISCUSSION

A review of the literature on experimental transplantation of tissues, and the results reported in this paper, lead to the conclusion that new-bone formation, following transplantation of various tissues to soft parts of the body, may occur as the result of either of two processes separately, or by a combination of the two. There is clear evidence that certain cells, when subjected to autogenous transplantation, may proliferate and form new bone. There is equally clear evidence that under certain circumstances the transplanted tissue does not itself form new bone, but that influences from within the transplant, by a process called induction, may produce an effect upon the cells of the host, causing the latter to produce new bone. Under other conditions, and with other transplanted tissues, it seems possible that both processes combine to form new bone, and that in such cases the new bone arises from both the cells of the transplant and of the host. This paper deals with a study of the formation of new bone under a variety of circumstances, and with an attempt, not always wholly successful, to differentiate in each case the processes responsible for the end product of bone.

It is clear that bone always arises as the result of the activity of cells which have differentiated from one variety or another of connective-tissue cells. When a cell has the ability to form bone, it is said to have *osteogenetic potency*. If this potency is brought into play, *osteogenetic activity* is recognizable; and, if this activity is elicited by influences from outside the cell, it is said to be *induced*, and the process is that of *induction*. The property of osteogenetic potency is shared by many of the connective-tissue cells of vertebrates; the conditions which lead to exhibition of this potency, or osteogenetic activity, have been the subject of many investigations, including those reported in this paper.

The method used in the observations here reported—that is, transplantation of tissues into the anterior chamber of the eye, and subsequent observation of the end result as the formation of bone at the site of the transplant—while it serves as a criterion of osteogenetic activity, does not necessarily discriminate clearly between osteogenetic activity on the part of the cells of the transplant and that on the part of the cells of the host. Such discrimination requires careful histological studies, as well as consideration of all of the conditions entering into the experiment. As an example, if devitalized tissue is implanted into the eye and bone formation results, this is clearly an example of induction, even though the discrimination by histological observation alone may be difficult. As has been seen in the above descriptions of experimental results, the nature of the end product—that is, whether a complete ossicle, with cortex and marrow, or osseous tissue alone is formed—may give a clue as to the nature of the process being observed. If the end result is *bone*—that is, an organ—*organotypic potency* has been called into play; if the end result is *osseous tissue* alone, the potency is *histotypic*. Either may conceivably be inherent in the cells of the transplant or induced in the cells of the host.

The evidence that new bone may arise from transplanted cells is clear. It is most striking in the case of tissue cultures[15, 42, 51] and from the experiments of Heinen[23], who transplanted the outgrowth from tissue cultures of bone into the anterior chamber of the eye, but there is much additional evidence which will be cited in the discussion which follows. The evidence that new bone may arise from the cells of the host, following transplants to soft parts and organs in which there is no possible contact with cells of the host previously concerned with osteogenesis, is no less convincing.

The theoretical considerations and main experimental observations bearing on these points may be summarized as follows. New-bone formation has been observed from not less than six different kinds of skeletal tissue transplanted by a variety of techniques[3, 8, 15, 21, 30, 41, 47, 48, 55]. The process appears to have been altered by many factors, such as whether the transplant taken was from an embryo, a young, or an adult animal; whether the transfer was autogenous, homogenous, or heterogenous; whether the transplants were fresh, refrigerated, or devitalized by freezing, drying, boiling, or chemical coagulation. The results of experiments on tissue transplantation are generally interpreted in the light of the following facts. Certain tissues in mammals, such as skin, transplanted during postnatal life from one location to another—that is, autogenous transplants—will survive and even proliferate and produce new cells. Skin, cornea, cartilage, and other less highly specialized types of tissue transplanted from one individual to another of the same species—that is, homogenous transplants—may survive for a period of time, but there is much doubt that normal mammalian cells will proliferate under such conditions[36].

With the exception of embryonic tissues and certain types of cancer cells, mammalian cells are absorbed and do not survive heterogenous transplantation (transplantation from one individual to another of a different species)[19]. Bone formation has been observed in embryonic and malignant tissue of various kinds three to seven months after heterogenous transfer[29].

The eye is probably no more favorable to bone formation than the subcutaneous region, the belly of a muscle, and many organs in which experimental and pathological bone formation has been observed. Although experimental heterotopic bone

formation has been produced in the eye by injections of formic acid into the vitreous body of rabbits[25], the process was not observed in forty-six control operations in rats as listed in Table II. Twenty-two autogenous specimens of miscellaneous connective tissues, such as muscle and fascia, did not produce new-bone formation either from the donor cells or from the eye after thirty days.

Dyer and Kelly observed new-bone formation in transplants of various soft-tissue tumors after three to seven months in the eye. Greene[20], who also studied transplantation of embryonic and normal tissues, noted that his transplants always underwent transformation into bone if they remained in the eye for a sufficiently long period of time. The negative results with muscle tissue and many other soft tissues in thirty days speak against the possible presence of osteogenetic cells in the tissue. However, this does not exclude the possibility that transplants of such tissues may induce new-bone formation after a longer period in the eye.

Periosteum: Schepelmann, Kolodny, and Polacco have reviewed the literature on the bone-forming potentialities of periosteum, beginning with the work of Bonome in 1886. Schepelmann observed that new bone was produced when the full thickness of the periosteum was transplanted to any visceral organ such as omentum, ovary, liver, and ureter. Kolodny and Riess emphasized the fact that transplanted periosteum from a young, growing individual usually produced new bone and concluded that the nineteenth-century controversy about the osteogenetic potency of periosteum arose because it was not generally realized that the negative results occurred only in transplants from adult or aged animals. The results reported in this paper add to this the finding that bone-forming potentialities of the adult periosteum could be activated before transplantation by a fracture of the underlying cortex. The activation occurred in less than twenty-four hours after the injury, and the periosteal cells promptly produced intramembranous new-bone formation.

This ability of the periosteum to become quiescent and morphologically indifferent in appearance and function in the adult, with the return of the original bone-forming function following an injury, is an excellent example of the phenomenon of *modulation*. The term "modulation", as distinguished from differentiation, describes reversible or temporary alterations in the functions of cells, without change in their potencies[7,62].

It has not yet been determined whether periosteum can produce new bone other than by the osteogenetic potency of its viable cells. Polacco reported positive results with supposedly non-proliferating homogenous transfers of periosteum. De Bruyn obtained no bone in twelve transfers of frozen periosteal tissue, but the osteogenetic activity of the tissue, if it came from adult animals, was probably not very great even when fresh. Data are needed on devitalized transplants of periosteum from young vigorously growing animals.

The foregoing experiments show that periosteum produces new-bone formation mainly from cells which have osteogenetic potency. Such cells were *histogenetic*, productive only of one tissue, and the special characteristic structure of the intramembranous type of bone formation. The end product of periosteum thus differed from that of other tissues, such as marrow, cancellous bone including endosteum and marrow, and cartilage tissue, all of which were *organogenetic* and produced an ossicle rather than a simple mass of tissue. Osteogenetic induction evidently leads to organogenesis, as will be described below.

Bone Marrow: It can be shown that a sample of autogenous bone marrow, carefully excised without attached bone spicules or endosteum, will produce new-bone formation following transplantation. Pfeiffer transplanted autogenous marrow of mice to the anterior chamber of the eye and also to the testes, and observed that myelogenous and hematopoietic cells died and disappeared from the graft, and presumably only the reticular cells survived. The reticular cells were assumed to have osteogenetic potency, or the capacity to transform into osteoblasts, by a process similar to that seen in mice treated with

estrogen[69]. The reticular cells of the bone marrow appear to have a decidedly different level of differentiation from that of the periosteum, since they showed potencies for the development, not only of bone, but also of cartilage and of hematopoietic bone marrow.

The bone-forming potential of homogenous transfers of marrow tissue has not been determined conclusively, but has been recently described in a related study on the blood-forming elements by Rekers, Coulter, and Warren. They observed bone deposits in homogenous transplants of marrow of adult rabbits to the anterior chamber of the eye, subcutaneous tissue, and muscle. Intravenous administration of homogenous marrow suspensions also produced new-bone formation in the walls of the small veins and capillaries in the lungs of adult dogs. De Bruyn transplanted to the thigh musculature of rabbits both autogenous and homogenous bone marrow which had been devitalized by freezing in liquid nitrogen or dry ice. Two out of twelve devitalized transplants produced new bone within three weeks. Whereas autogenous transplants of bone marrow appear to give rise to new bone by survival and proliferation of reticular cells, it is less clear that this is the case with homogenous transplants. The experimental findings can best be explained by the assumption that both osteogenetic activity and induction can take part in the reaction to transplanted bone marrow.

The Fracture Hematoma: Autogenous transplants of organizing blood clot excised from the fracture site did not produce bone within thirty days. This would seem to be further evidence against the theory of Bier that hematoma fluid contains an osteogenetic factor.

Cancellous Bone: Because of the difference in cellular composition of the tissue and the variability of the results reported following transplantation of bone to soft parts, it is very important to examine separately the activity of cancellous bone which contains reticular cells of the bone marrow and a sample of compact cortical bone which contains no bone marrow.

The fate and activity of cancellous bone tissue of adult animals transplanted to soft parts have been described in a large number of clinical and scientific papers; these have been reviewed by Ghormley and Stuck and others[32, 43]. There is general agreement that the bone cells (osteocytes) do not survive even in an autogenous transplant[48]. The main question has been the source of the new bone produced around the graft; whether the new bone comes only from an outgrowth of cells which are linear descendants of osteoblasts, or whether the bone develops by means of an "osteogenetic substance" supplied by the donor's tissue which induces new-bone formation in the proliferative inflammatory connective-tissue reaction of the host.

Bisgard, Kimball, and Mosiman observed new-bone formation in autogenous transplants in the anterior chamber of the eye in rabbits and guinea pigs. Kimball compared the fate of autogenous transplants with homogenous and heterogenous transfers, and submitted the thesis that both types of transfer, in which no part of the transplant would be expected to proliferate, did produce new bone. Osteogenesis, however, occurred in only one or two heterogenous transfers and the end product was always scant. Under these circumstances, osteogenesis appears to have been initiated by induction.

Cortical Bone Transplants: Bisgard transferred autogenous cortical bone to the anterior chamber of the rabbit's eye and the results, similar to those reported herein, were the production of a very feeble reaction. Only the transfers of compact bone which were penetrated by blood vessels from the host and which had undergone some absorption produced new bone. Some of the thinner slices of solid cortex which had no interstices did not produce new bone within thirty days. Cortical bone appears to be a relatively poor inductor.

Transplants of Devitalized Bone: Bisgard devitalized six samples of bone tissue by boiling and transplanted them to the anterior chamber of the eye in rabbits. New-bone formation was observed in three instances. Kimball transferred five samples of boiled homogenous bone to the anterior chamber of the eye, and observed "marginal new-bone

formation" in one instance. Autogenous bone, devitalized by freezing in liquid nitrogen or dry ice, by alcohol, formalin, or heat, was transplanted to the thigh musculature of rabbits by Nageotte, Polettini, Röhlich, and De Bruyn, and all reported new-bone formation in a few instances. Although it is unfortunate that all of these transfers were made in rabbits' muscle, which is highly susceptible to ectopic bone formation, the results suggest that the new-bone formation was produced by induction. Orell also reported positive results with subcutaneous transplants of devitalized bone. Osteogenesis was initiated if the graft was vascularized and penetrated by perivascular primitive connective-tissue cells from the host. The time interval was the main difference between the appearance of the new bone in fresh and dead bone grafts. Observations by Hancox suggest that this may be due in part to a longer period for adaptation, and for the beginning of absorption by the host. Short capillary buds from the host joined and fused with the cut ends of the vessels of the graft in embryonic bone transplants to the chorio-allantoic membrane within five hours. Similar boiled bone transplants did not become vascularized in a comparable manner and showed no vascularization as late as forty-eight hours after transplantation. Kiehn and his associate studied the vitality of transplants of cartilage and bone with the use of radio-active phosphorus and found evidence of ionic exchange less than twenty-four hours after the tissue had been transferred to the subcutaneous region, but the graft did not show maximum assimilation of P^{32} until its "blood supply" had developed. Devitalized transplants showed "depressed assimilation" of phosphorus for about one week, apparently lacking the early fluid exchange developed by fresh autogenous grafts.

Epiphyseal Cartilage and Articular Cartilage: The foregoing experiments show definitely that the hyaline cartilage from the epiphyseal lines, or from the articular surfaces of young animals, will consistently produce new bone following surgical transplants to the anterior chamber of the eye. It is doubtful that the chondrocytes have the potency to transform into osteoblasts or bone tissue in mammalian species, although this has been a debatable point in lower animals[10, 27, 29]. It is difficult to identify chondrocytes after the lacunae are opened. In the view of many recent investigators [21, 31, 56, 57], the escaped cells apparently degenerate and become absorbed.

Convincing evidence of osteogenetic induction has come from observations upon the reaction of the host to transplants of young cartilage tissue. Gordon and Warren and Lacroix have reviewed the literature and presented experiments which show that fresh or devitalized cartilage contains a factor which will induce new-bone formation in the connective tissue with which the donor cells become attached to the vascular system of the host. In observations similar to those by Levander [33] and Röhlich upon bone-to-muscle transplants, Lacroix noted that the new-bone formation began on the margin of the cartilage and only later grew into the substance of the donor tissue. He proposed the term *organizer phenomenon* for this process. Levander [34] interpreted this process as an example of *induction*. Both terms come from the field of experimental embryology and are based on the postulate that the earliest differentiation and development of tissues depends upon the interaction of influences, physical and chemical, which one tissue exerts upon another in contact with it [63].

Fracture Callus: Fibrocartilaginous callus excised from the fracture gap produced new-bone formation earlier and more vigorously than any of the other tissues. The transplants contained spindle-shaped connective-tissue cells, which may reasonably be suspected of being linear descendants from osteogenetic cells of the endosteum or the reticular cells of the bone marrow, both of which have been shown to produce cartilage and bone in tissue culture [18, 51], but the end product was exactly the same as that of transfers of pure samples of growing cartilage. An autogenous transplant of these cells within a short time produced a whole new bone with a hematopoietic marrow. The transplants of fibrocartilaginous callus always contained islands of fibrocartilage and hyaline cartilage, which may have

survived transplantation but were never observed to proliferate or multiply. Instead the transplant was rapidly absorbed. The new-bone formation began in the absorption spaces *inside* the inner vascular layer of the envelope of connective tissue formed by the host. The same result was observed when all of the cells were destroyed by boiling or freezing of the transplant prior to transfer to the anterior chamber of the eye. This was observed only after a period of four to five weeks, and with a poor yield of new bone. These observations suggest that young growing cartilage will confer osteogenetic potency upon ingrowing mesenchymal cells. The process was just as active in fresh homogenous as in fresh autogenous transfers, indicating that cellular growth or genetic compatibility were not essential for induction.

Bone Banks: Experimental transplantation of bone to subcutaneous regions, muscle, and all kinds of soft-tissue organs as well as to the anterior chamber of the eye has invariably been found to show that a fresh autogenous graft of cancellous bone has greater osteogenetic activity than fresh or preserved bone. The latter, however, depending somewhat upon how long the graft had been stored or how harshly it had been treated for preservation, have shown osteogenetic activity in a small percentage of transfers when implanted in soft parts which had no possible communication with the skeleton. When grafts are implanted in bone defects, the osteogenetic tissues of the host show a specific and *striking affinity* for the inert substance of cartilage or bone and will grow into the donor tissue until it is completely incorporated and absorbed. After the process has become initiated, it has been impossible, either in experimental or clinical investigations, to distinguish between fresh autogenous and devitalized homogenous bone tissue transferred to a bone defect. The results suggest that the substance of cartilage and bone tissue leads to osteogenetic induction, upon which the osteogenetic process and "creeping substitution" depend when the graft is replaced by new bone.

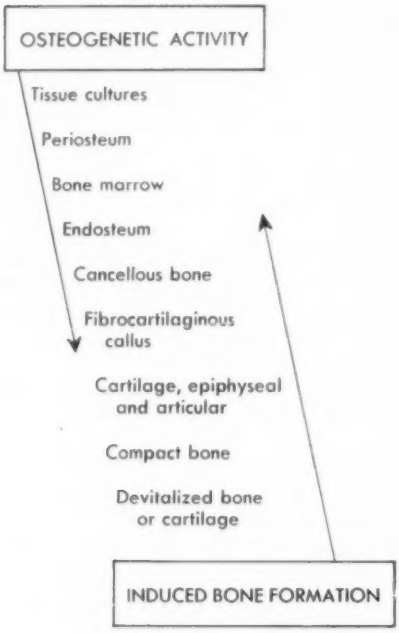

FIG. 12

Diagram showing a comparative analysis of the osteogenetic activity and the probability of source of the new bone produced by different types of transplants of skeletal tissues.

Tissue Extracts: Ectopic bone formation has been described in rabbit muscle injected with alcoholic extracts of bone [1, 33, 34, 35, 52, 61, 66], bone marrow [1, 4, 35, 61], and growing cartilage [31]. Osteogenetic induction apparently occurs readily in muscle tissue of the rabbit. Martin Lagos and Zarapico Romero, Heinen and his associates, and Hartley and his coworkers have shown that this species will produce ectopic ossification following injections of alcohol alone or of other chemical irritants, with nearly as high a percentage of positive results as reported with tissue extracts. Eskelund and Plum used the site of a healing fracture of the femur of the rat, but obtained equivocal results. Attempts to extract the osteogenetic factor from the alcoholic solutions have thus far failed [66], but the crude fatty-acid fraction has been reported to carry the greatest "osteogenetic activity" [35]. The situation with respect to extracts of bone remains for the present that, while the experimental and histological evidence as presented and summarized in this paper favors the concept of induction

of bone formation, isolation and characterization of "inductor substances" from extracts has not been satisfactorily accomplished.

SUMMARY

As has been indicated above, it is not always possible to determine whether bone formation, following transplantation of a tissue to a favorable environment, is the result of proliferation and osteogenetic activity of transplanted cells, or whether the cells of the host, under the influence of induction as a result of the transplant, are responsible for the appearance of new bone. In an attempt to resolve this difficulty and for the purposes of exposition, there is presented a diagram (Fig. 12) which illustrates the probability that one or both of the mechanisms are operating in any given instance.

In the upper portion of the diagram are shown those tissues in which new-bone formation is almost certainly the result of the osteogenetic activity of the transplanted cells (tissue cultures, periosteum transplanted to the eye); in the lower portion are devitalized tissues which cannot conceivably give rise to new bone by proliferation, and which form one of the strongest arguments for the phenomenon of induction. Between these extremes are various tissues which may act by one or both mechanisms, and an attempt has been made to arrange these in some semblance of order to illustrate the probabilities in the case of each tissue. At the middle of the scale it appears highly probable that cancellous bone and fibrocartilaginous callus may proliferate with formation of new bone and also induce bone formation by their effects upon the cells of the host.

There is thus proposed a resolution of a basic problem of osteogenesis by acceptance of the postulate that post-foetal new-bone formation, instead of depending solely upon one of the two mechanisms which have been proposed, may occur through the effect of either of these mechanisms, or by a combination of the two.

CONCLUSIONS

1. New-bone formation, in the anterior chamber of the eye, has followed autogenous transplants of periosteum, bone marrow, cancellous bone, cortical bone, fibrocartilaginous callus, epiphyseal cartilage, and articular cartilage. Similarly, new-bone formation has followed transplants of homogenous epiphyseal cartilage to the anterior chamber of the eye.

2. An attempt has been made in each instance to determine whether the new bone formed in the anterior chamber of the eye originated from survival and proliferation of the transplanted cells, or whether it resulted from induction due to contact with the transplanted tissues.

3. The evidence from these studies indicates that periosteum, bone marrow, and some of the elements of cancellous bone and of fibrocartilaginous callus may survive and proliferate following transplantation, and give rise to new bone directly.

4. Induction of new-bone formation, originating from the cells of the host, but induced by contact with transplanted tissues, was brought about by transplants of devitalized fibrocartilaginous callus. Induction also appeared to be responsible for new-bone formation following transplants of epiphyseal and articular cartilage, and it appeared at least to play a part in the formation of new bone following transplants of cancellous bone.

5. As to periosteum, new-bone formation followed transplants in rats of three weeks of age, but did not result from transplants of periosteum from normal rats approximately one year of age. New bone was formed, however, when periosteum from the region of a fracture was transplanted to the eye as early as twenty-four hours after the injury was produced experimentally.

6. Only compact bone without cartilage or bone marrow was produced by transplants of periosteum. Autogenous implants of cortical bone led to scant deposits of new bone on the surface of the implants after the fourth week in the eye. Transplants of bone marrow,

cancellous bone, fibrocartilaginous callus, epiphyseal cartilage and articular cartilage resulted in the formation of ossicles complete with cortex and hematopoietic marrow.

7. Autogenous fibrocartilaginous callus, devitalized by boiling or by freezing with carbon dioxide, when transplanted to the anterior chamber of the eye, led to deposition of new bone on the surface at four to five weeks, followed by invasion of the devitalized implant by bone arising from the tissues with which the implant was in contact.

8. Autogenous transplants of muscle, fascia, tendon, capsular ligament, urinary-bladder epithelium, ureter, fracture hematoma, semilunar cartilage, and ear cartilage failed to lead to formation of bone within four weeks.

9. The bearing of these findings upon the concepts of osteogenetic activity and induction, as well as upon old conceptions of the function of a bone graft, is of particular interest and suggests that "creeping substitution" is essentially a process of new-bone formation by induction.

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DISCUSSION

DR. ROSCOE S. MOSIMAN, NEW ORLEANS, LOUISIANA: Concerning the basic concepts of bone formation presented in this article we can have no major disagreement. It seems that there are both prenatal and postnatal influences which can modulate the formation of bone from tissue cells without bone being previously present. For example, consider the initial embryonal force which preforms skeletal elements from undifferentiated mesenchymal cells. The existence of ectopic bone in aortic plaques and other areas is one instance of postnatal factors. The results of Heinen's[b] alcohol-injection experiments demonstrate another postnatal effect. Heinen has produced bone in rabbit muscle by means of alcohol injection with a frequency which throws grave doubt upon the importance of much previous alcoholic-extract experimentation. The fact that ectopic bone is produced by such a necrotizing agent allows consideration of the possibility of an inductor mechanism released by cellular death. However, Urist and McLean state that if devitalized tissue is implanted into the eye and bone formation results, this is clearly an example of induction. We would suggest that the nature of the "inductor" may be in considerable doubt and must meet the same exacting questions that claims for alcoholic extract have met in the past.

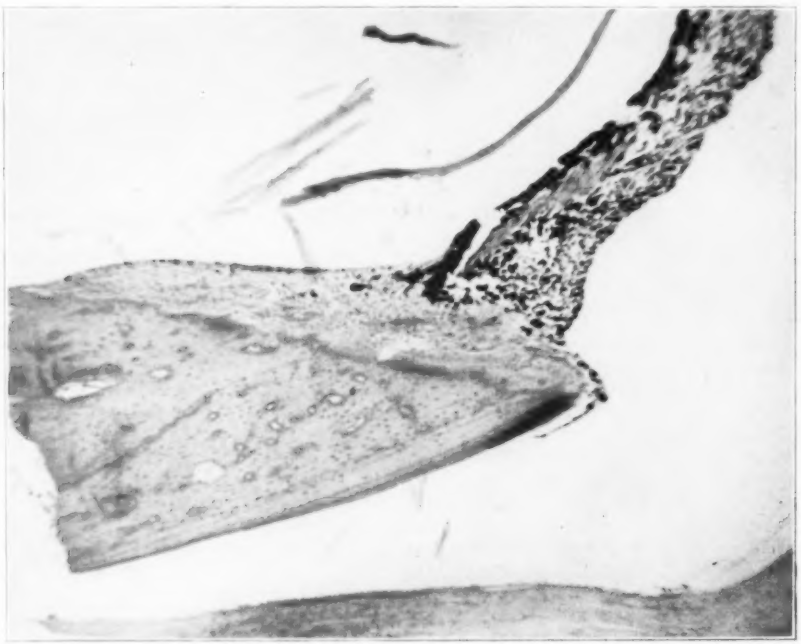

FIG. 1-A

Photomicrograph (× 30) of an autogenous chip of bone implanted in the anterior chamber of the eye nine days previously. The general structure of guinea pig cortex and the relationship to the iris with its heavily pigmented cells are shown. Early new-bone growth can be seen along the juncture of bone and iris.

We agree more emphatically that living tissue cells, including bone cells, can be transferred autogenously and remain capable of proliferation. In making this statement, we can offer as justification some of our own experimental results.

Our efforts have been directed during the past two years to: first, an evaluation of the transplant method in which the anterior chamber of the guinea pig's eye is used; and second, an application of this method to the study of bone-bank bone. For this purpose we have implanted autogenous bone from the guinea pigs' own fibulae into approximately 125 anterior-eye chambers. These have allowed the conclusion that 93 per cent. of such cortical implants will result in bone growth, usually beginning within two weeks after implantation. The bone-bank material has been studied with forty-five implants each of boiled bone, acetone-fixed bone, deep frozen bone, and merthiolate-preserved bone.

The autogenous cortical implants follow a predictable sequence of events with considerable uniformity. They can be watched through the transparent cornea, except for the first few days when there is clouding of the cornea due to the operative trauma. The gross changes which attend a successful "take" are easily seen; they consist in gradually increasing capillary supply to the implant, rounding of its edges, pink color, and definite increase in size. Those implants of dead bone which will be described later remain sharp-edged, white, are devoid of blood supply, and do not grow.

The microscopic findings parallel the gross observations. The fresh autogenous cortical implant is caught up on the first day in a light fibrin mesh, a few inflammatory cells being present. During the first few days cells disappear from the periphery of the implant. Simultaneously cells which do not seem to stem from eye tissues appear in the fibrin surrounding the implant. Their source may be the implant. The implanted chip is usually reached by capillaries from the iris or the cornea or both by about the sixth day. Bone growth starts at about this time and proceeds rapidly; it is appositional in type in that it proceeds directly from the surface of the old bone.

The next occurrence of importance is the appearance of the series of changes classically described by Phemister and others as "creeping substitution". This consists in invasion of the old Haversian systems and fracture lines by capillaries which seem to dissolve the old bone around them. We have not seen any multinucleated giant cells in this process. After the vascular channel has been enlarged, the peripheral cells seem to proliferate new bone which then lines the channel and slowly replaces the old bone of the original implant.

As time passes and the bone grows until it may fill half of the anterior chamber, one can section the eye and find that somewhere in the bony mass the original implant is still undergoing creeping substitution

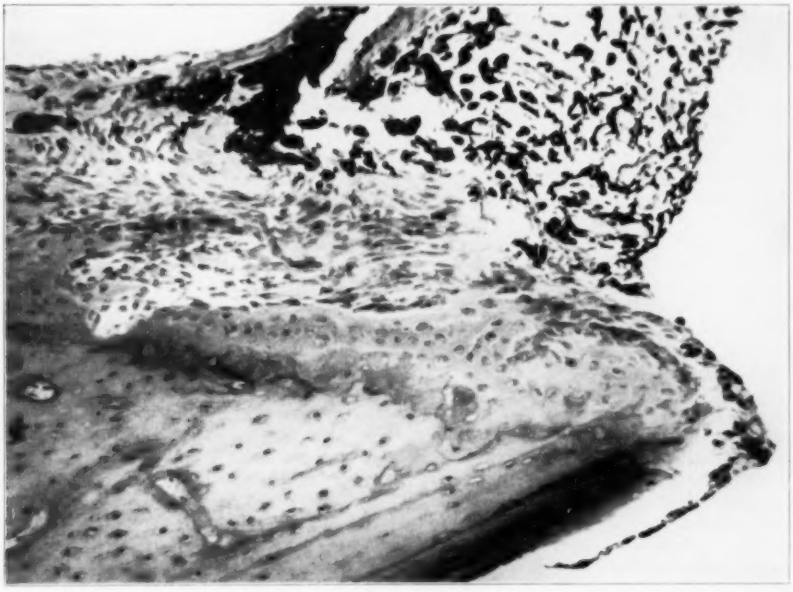

FIG. 1-B

High-power photomicrograph (× 80) of the tip of the implant in Fig. 1-A. This reveals the details of the early new-bone formation from osteoblastic proliferation and emphasizes its appositional characteristics.

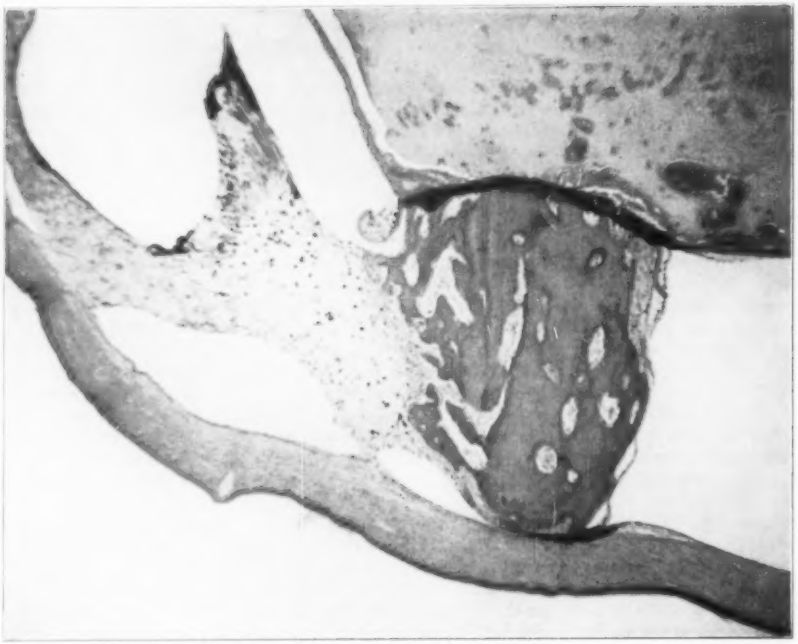

FIG. 2-A

Photomicrograph (× 30) of an autogenous chip which has been implanted in the anterior chamber for three weeks. The original chip is notable for its lacunae, which are empty of osteocytes. The new bone is loosely trabecular in structure and seems to be nourished both by eye capillaries and by the aqueous humor.

The mass of appositional bone which has formed in roughly concentric lamellation of the trabeculae may be twenty or thirty times as great as the volume of the implant. We feel that this bone growth and creeping substitution both result from the simple transplantation of bone tissue with living cells; and, as a corollary, that a fresh autogenous bone graft is vastly more important than a dead framework for invasion by bone from the area in which it is placed. It serves as a tissue transplant, as a source of new bone, and is thus truly osteogenetic.

The bank bone studied by this method gave markedly different results. Boiled bone was used since, if bone growth occurred following its implantation, such growth could result from the effects of the operation as well as the effects of simple bone salt. Acetone-fixed bone was used since cold acetone fixation kills cells but leaves much of the phosphatase mechanism intact. Deep frozen bone, prepared by the method of Bush[5], was used. Its cells would probably be killed by the freezing but chemically it would remain nearly identical with living bone. The enzymes, proteins, and salts would all be in nearly correct chemico-anatomical relation to one another. Bone preserved in merthiolate, by the method of Reynolds and Oliver[6], was also used to provide dead bone as well as a chemical irritant.

In each of these types of bone histological studies were carried out at intervals of three, six, nine, and twelve days, and two, four, six, eight, and twenty weeks. Thus they were observed both early and late. At no time did any of these implants, forty-five of each type, show any evidence of bone growth, creeping substitution, or even absorption. They remained as inert foreign bodies in the eye. Approximately 70 per cent. were embedded in the lens. This is a frequent fate of a sharp-edged foreign body freely moved by the iris in the anterior chamber. The remainder became encapsulated in light mature fibrous tissue and underwent no visible change. They were not osteogenetic.

In view of these results we are completely unable to explain some of the results reported by Dr. Urist and Dr. McLean. For example, in twelve instances of fresh cortical-bone implantation in their study "there were no positive results in less than twenty-eight days, but a scant deposit of new bone appeared in two instances after the fourth week in the eye". Also, in the study of boiled fibrocartilaginous callus, two of three samples produced bone growth, and with frozen fibrocartilaginous callus one of three samples produced bone

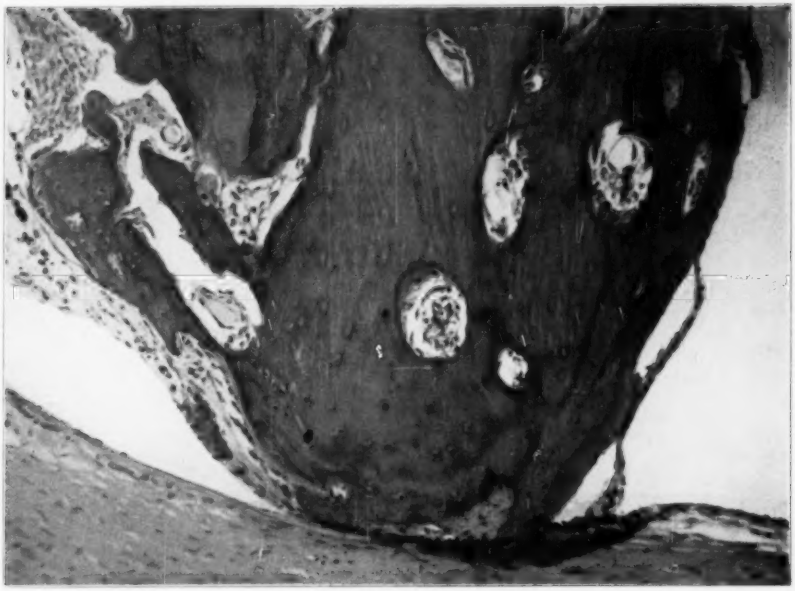

FIG. 2-B

High-power photomicrograph (× 80) of a portion of the implant in Fig. 2-A, showing acellular old bone, proliferating new bone, and the vascular erosion of the original chip. This erosion is the beginning of the process of creeping substitution.

growth. These findings would tend to show that boiled callus material is more osteogenetic than frozen callus and both are more osteogenetic than is fresh autogenous cortical bone in the anterior chamber of the rat's eye.

It must be remembered that Urist's and McLean's rat-eye experiments and our own use of the anterior chamber of the guinea pig's eye are not at all parallel. Not only were different animals used, but the approaches to the problem also differed considerably. We have tried to find out what happened to fresh autogenous cortical bone in the anterior chamber of the eye. Would it grow, cause growth, act as a foreign body, and above all, would the reaction be uniform enough to be of value as a method of study? Urist and McLean have shown what happened to many different types of materials in the anterior chamber of the rat's eye.

The major discrepancy between the two experiments is in the behavior of cortical bone. Such periosteum-freed bone is not pure tissue. It contains neural elements, vascular elements, and fibrous elements, as well as osteocytes and osteoblasts. However, in the guinea-pig experiments, as previously stated, bone grew successfully 93 per cent. of the time. In the paper under discussion cortical bone did not give rise to early bone growth in any of the twelve instances of implantation. This difference has not been explained.

Concerning the findings as to the growth potential of periosteum, especially the observation that adult periosteum is not osteogenetic but that adult fracture periosteum after a few days is highly potent, more effort may be expended. It is an interesting speculation to consider the possibility of stripping periosteum and then using it after a certain interval as a delayed grafting material in place of bone.

Also of great interest is the finding that hyaline joint cartilage obtained without bone-cell elements produced bone in the eye with such considerable uniformity that all nine transfers showed new bone after three weeks. Early new-bone growth of this type allows at least two interpretations. One is that the tissue culture of cartilage can grow bone. The other is that held by Urist and McLean, that cartilage contains a chemical inductor which causes the eye cells to grow bone. This question may be illuminated by future experiments using the anterior chamber of the eye.

In closing it should be pointed out for the benefit of those who may use the anterior chamber of the eye that there are pitfalls in this as in any biological method. It is true of guinea pigs and human beings that long-term infection or excessive trauma to the eye will cause bone formation. This is termed a reaction of degeneration in the eye and is well recognized by ophthalmological pathologists. Such bone growth we have observed to occur late, and often at a distance from the implant which has been used. It is not a source of confusion in the early bone formation which we have reported. It is usually peripheral and occurs in eyes in which the internal relationships have been destroyed by trauma. It may occur without any implant being

FIG. 3-A

Photomicrograph (× 30) of an autogenous cortical implant of eight weeks' duration. The amount and structure of the new bone is apparent. The old cortical remnant is entirely acellular.

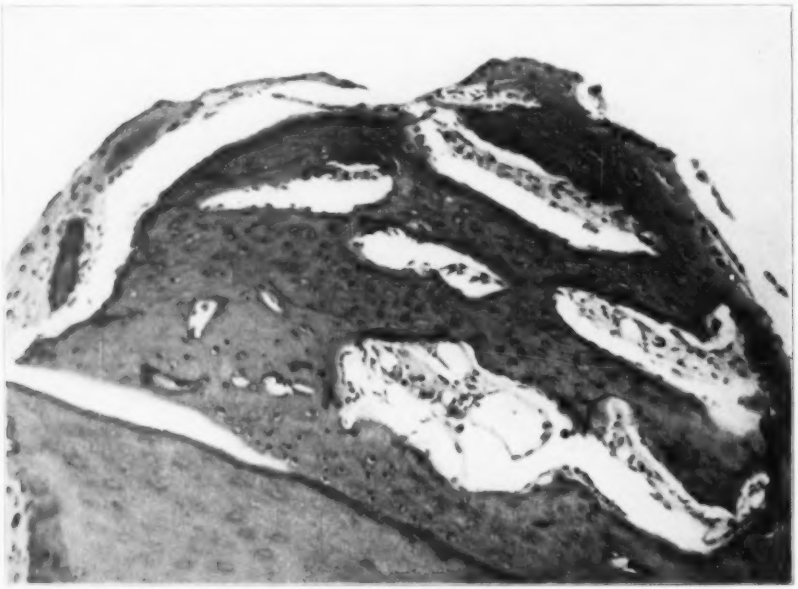

FIG. 3-B

High-power photomicrograph (× 80) of the margin between new and old bone in the implant shown in Fig. 3-A.

FIG. 4-A

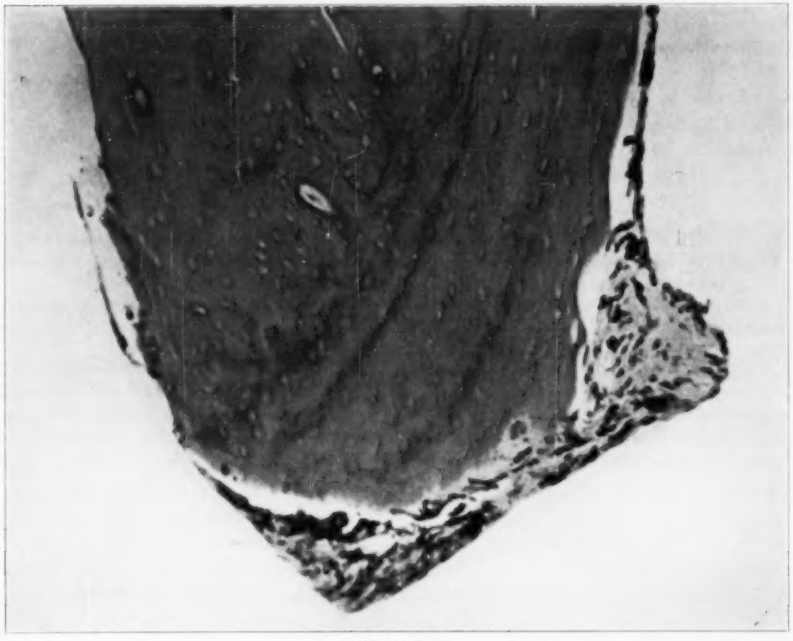

FIG. 4-B

(*Legends on page 476*)

(*Continued from page 475*)

FIG. 4-A: Photomicrograph (× 32) of a typical implant of bank bone. It has been implanted in the anterior chamber of the eye for four weeks. In appearance, it could pass for any of the types of bone studied: boiled, deep frozen, acetone-fixed, or merthiolate-preserved. It is deep-frozen autogenous bone. The chip is acellular. There is no new bone. A mature fibrous capsule consisting of eye cells with iris pigment is present.

FIG. 4-B: High-power photomicrograph (× 100) showing detail of dead deep-frozen acellular bone without new-bone formation as shown in Fig. 4-A.

present. We do not mean to imply that the results under discussion are due to this reaction, but merely to point out the complications to others who may use this excellent method of investigation.

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DR. URIST (closing): Time does not permit a comparative analysis of our results and the results of the experiments of Kimball, Mosiman, Wickstrom, and others of the New Orleans group who have attempted to evaluate refrigerated or bank bone for bone-graft operations. We have concentrated our investigations upon the mechanism of osteogenesis by the process of induction. Our observations suggest that homogenous, heterogenous, and devitalized bone grafts are osteogenetic, although such transplants do not supply proliferating osteoblasts. Excessive boiling or prolonged storage probably destroys a large part of the osteogenetic inductor substance. Compact bone tissue from the mid-shaft of the fibula is relatively inactive compared with cartilage and other motor-skeletal tissues which we have transferred to the anterior chamber of the eye. There is no doubt that autogenous bone shows greater osteogenetic activity than homogenous or devitalized bone when transferred to soft parts, but there is still a question whether one type of bone graft is much better than another when transplanted into a fresh bone defect. Our experience indicates that the success of a bone-graft operation depends mainly upon the activity and proper preparation of the host bed for implantation of the graft or donor tissue.

DISCUSSION

ELECTRON-MICROSCOPE STUDY OF BONE

(*Continued from page 435*)

altogether; but, if it should hit the crystal, there is no more crystal. I admit that the blending method is moderately gross in this treatment, but it is the best thing we have found. Perhaps in the future we will be able to find another method; we have tried others without success.

The cement substance, as a product of the bone cell, differentiates this cell from other cells. Chondroitin sulphate, a mucopolysaccharide, has the characteristics of an exchange resin, and it binds first calcium, then, in turn, phosphate, and then again calcium, as has been shown by Boyd and Neuman.

Recently Lightfoot and Coolidge have shown that about 35 per cent. of the protein is in the cement substance as a non-crystalline part. The cement substance contains protein along with acid mucopolysaccharides, carbonate, sulphate, and chlorides.

I agree that the basic problem is to discover what makes the osteoblast produce this bone matrix rather than some other sort of matrix such as one finds in cartilage, tendon, or fascia.

THE SENSORY NERVES OF THE HIP JOINT*

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The difficulties found in the resection of the sensory nerve branches to the hip joint, a surgical procedure suggested in 1945 by Tavernier and Godinot for the treatment of osteo-arthritis, and studies of the results obtained have drawn the attention of orthopaedic surgeons to the nerve supply of that joint.

Precise information on the innervation of the coxofemoral articulation and on the origin, number, and topography of the articular branches is so scant that the surgical procedure of articular denervation is rendered difficult and uncertain. The possibility suggested by some surgeons that there may be anatomical variations in those branches makes the results of neurectomy still more unpredictable.

A review of the literature reveals that the majority of writers consider the ventral aspect of the capsule of the hip joint to be innervated by twigs from the obturator nerve; others ascribe its innervation to fibers from the femoral nerve, to twigs from both nerves, or to twigs from the accessory obturator nerve in cases where the latter is present.

With the single exception of Chandelux, writers on the subject are agreed that the hip joint is supplied by the obturator nerve. This is variously described as taking place through a common branch to the pubocapsular ligament and the musculus obturator externus (Rüdinger); by a filament to the incisure of the acetabulum (Duzéa); by branches arising either from the anterior or from the posterior branch of the obturator nerve (Sadovskii); from the posterior branch only (Guesselevitch; Billet, Vincent, and Gaudefroy); by two or three filaments arising from the obturator nerve, usually in the pelvis (Minne and Depreux; van Wien and Moyson; Poulhés, Planel, and Gédéon); frequently by a twig originating from the posterior branch of the obturator nerve within the subpubic canal (Pellanda); from the trunk of the nerve within the canal (Gardner); either from the trunk or from the terminal branches of the obturator nerve (Kaplan).

The innervation of the anterior aspect of the capsule by an accessory obturator nerve is indicated by Billet, Vincent and Gaudefroy, and by Pellanda, Gardner, and Kaiser. On the other hand, Eisler, Paterson, Ancel and Sencert, Jamieson, Bonniot, and Sousa found accessory obturator nerves which did not supply filaments to the coxofemoral articulation.

According to Duzéa, the anterior aspect of this joint is also supplied by an internal lumbar branch and by an external lumbar branch.

As regards the contribution of the femoral nerve, its articular twigs are described as arising from one or another of the muscular branches of that nerve. Thus the capsular innervation is described as supplied by a plexus formed by three filaments arising from the muscular branches of the femoral nerve (Rüdinger, 1857); by a direct branch of the femoral nerve (Duzéa, 1886); by a filament from the nerve to the pectinaeus muscle (Chandelux, 1886); by two branches from the femoral nerve (Sadovskii, 1933; Guesselevitch, 1934); by a filament from the nerve to the rectus femoris (Billet, Vincent, and Gaudefroy, 1947); by a filament from the internal musculocutaneous nerve (Pellanda, 1948); by a branch from the trunk of the femoral nerve or from the nerve to the pectinaeus (Gardner, 1948); or from the trunk of the femoral nerve or the nerve to the rectus femoris (Poulhés, Planel and Gédéon, 1949).

* An abstract of this study, which is part of a thesis, was read at the First Congress of the Sociedad Latino-Americana de Ortopedia y Traumatología, Montevideo and Buenos Aires, December 1950.

FIG. 1

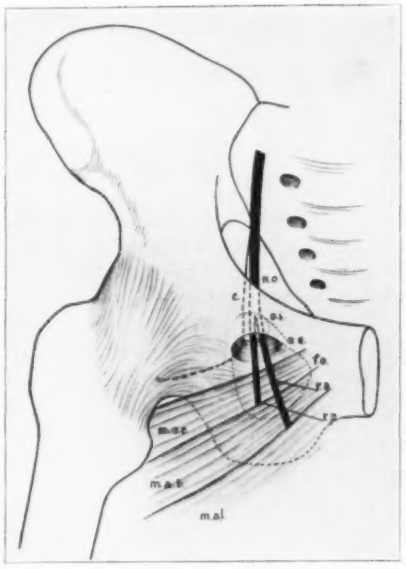

FIG. 2

Fig. 1: Case 24. Male, mulatto, right side. The capsular branch *c* arises from the posterior branch of the obturator nerve, at the level of the external orifice of the obturator canal, and courses over the anteromedial aspect of the capsule before perforating it close to its insertion in the femur.

Fig. 2: Case 7. Female, negro, right side. The capsular filament *c* arises in the pelvis from the trunk of the obturator nerve, passes through the canal and perforates its inferior wall to reach the capsule, proceeds in the latter, and plunges deeper in it at a point equivalent to that shown in Fig. 1.

The articular filaments from the femoral nerve have been described by many of these investigators as following the course of the vessels. They consider as the most important for the anterior aspect of the coxofemoral joint the branches arising from the obturator nerve.

The posterior aspect of this capsule is innervated by two filaments arising from the ischiatic nerve and one from the inferior gluteal nerve (Rüdinger); Duzéa, Chandelux, Guesselevitch, Pellanda and van Wien and Moyson attribute the innervation to branches from the ischiatic nerve or sacral plexus and from the nerve of the quadratus femoris; Sadovskii found that it originated from the ischiatic and superior gluteal nerves. Billet, Vincent, and Gaudefroy and Gardner describe the innervation as taking place from the nerve only to the musculus quadratus femoris.

MATERIAL

One hundred and twenty-four formalin-fixed specimens, all taken from adults, have been dissected since March 1946. Ethnic derivation and sex were not taken into consideration. Fifty specimens were studied by the ventral approach to investigate the possible supply; in fifty-three specimens the sacral plexus and its branches were visualized by the dorsal approach; and in twenty-one the participation of the femoral nerve was further investigated.

ANATOMICAL FINDINGS

We shall consider the number and types of articular branches and their origin from the trunk or from branches of the obturator nerve in relation to the obturator canal, as well as their relation to the nerve of the external obturator muscle.

FIG. 3

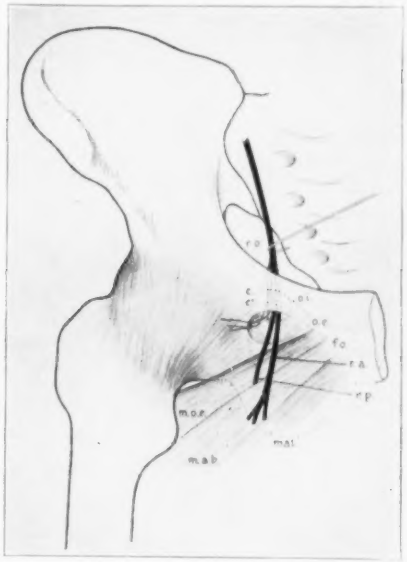

FIG. 4

Fig. 3: Case 46. Female, negro, right side. There are two capsular branches: one, *c*, arises from the posterior branch of the obturator nerve in the middle of the canal, perforates its lateral wall, courses among the fibers of the anteromedial aspect of the capsule, and finally terminates in the latter. The other branch, *c'*, which runs over the capsule, parallel and distal to filament *c*, also arises from the posterior branch of the obturator nerve, but at the level of the external orifice of the same canal.

Fig. 4: Case 17. Male, white, right side. There are two capsular branches: Branch *c* arises from the distal end of the trunk of the obturator nerve at the level of the internal orifice of the canal, passes through the latter, and reaches the upper portion of the capsule, where it bifurcates. Capsular branch *c'* arises from the posterior branch of the obturator nerve at the level of the external orifice of the subpubic canal, reaches the capsule, and courses above branch *c*.

Number of Articular Branches

In forty-nine of fifty cases the anterior aspect was supplied by branches from the obturator nerve, while in the last case it received its innervation from the accessory obturator nerve. Of these forty-nine cases, there was a single articular branch in thirty-three (67.34 per cent.), two in fourteen cases (28.57 per cent.), and three in two cases (4.08 per cent.).

Types of Articular Branches

The articular twig or twigs arising from the trunk or from the branches of the obturator nerve ended either in the anterior aspect of the capsule (capsular branch), or penetrated into the acetabular notch (acetabular branch).

Of the thirty-three cases with a single articular branch, the twig was capsular in twenty instances and acetabular in three (Fig. 10); in the remaining ten cases, the twig bifurcated into a capsular and an acetabular filament (Fig. 5).

Of the fourteen cases with two articular branches, one was capsular and the other acetabular in thirteen instances; in the remaining case both branches were capsular (Figs. 3 and 4).

In the two specimens with three articular branches, two twigs were capsular and the other acetabular.

In our forty-nine specimens, the articular branches took origin from the trunk of the obturator nerve (Fig. 9) in 71.64 per cent. of cases, from the posterior branch in 25.37 per cent., and from the anterior branch in 2.98 per cent.

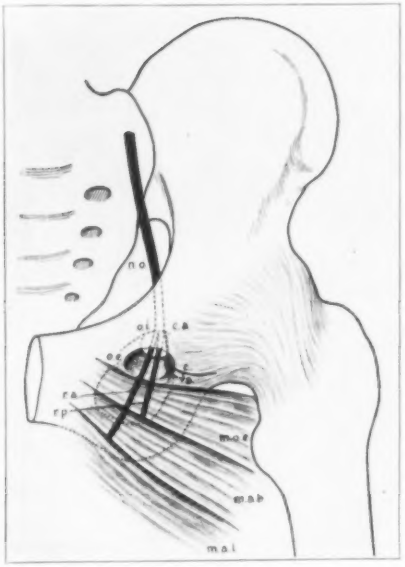

FIG. 5

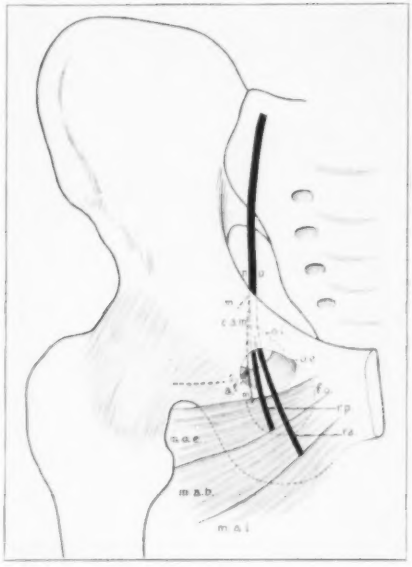

FIG. 6

Fig. 5: Case 50. Female, negro, left side. The articular branch, *c.a.*, arises from the trunk of the obturator nerve at the level of the internal orifice of the homonymous canal; just before reaching the external orifice it bifurcates into a capsular filament, *c* (which leaves by the latter opening and goes into the capsule), and an acetabular branch, *a*, which perforates the lateral wall of the canal to reach the acetabular incisure.

Fig. 6: Case 9. Male, mulatto, right side. About 1.5 centimeters proximal to the internal orifice of the obturator canal a nerve trunk, *c.a.m.*, takes origin from the obturator nerve, courses through the canal, and trifurcates into: acetabular, *a*, capsular, *c*, and muscular, *m*, branches; the last of these penetrates the external obturator muscle.

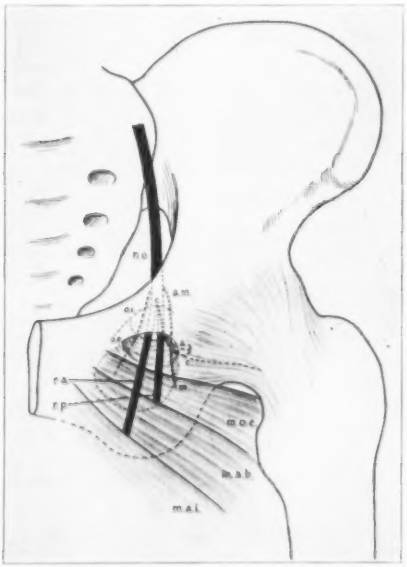

FIG. 7

(*For legends see page 481*)

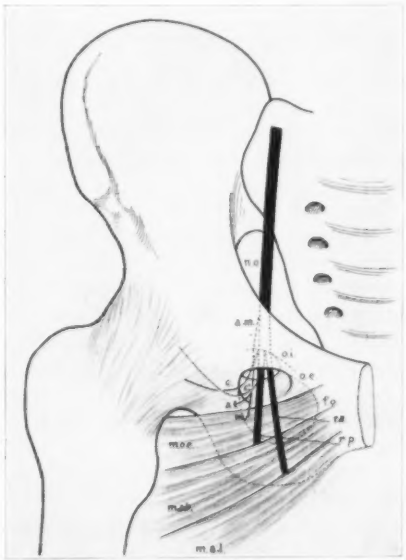

FIG. 8

Fig. 7: Case 16. Male, white, left side. This specimen presents two capsular branches. One, *c*, arises at the bifurcation of the obturator nerve, close to the internal orifice of the homonymous canal, perforates the anterior wall of the latter near the external opening, and reaches the articular capsule. The other branch, *a.m.*, arises from the trunk of the obturator nerve in the pelvis, penetrates the canal, and bifurcates into acetabular filaments, *a*, and muscular filaments, *m*; the latter leaves by the external orifice and ends in the external obturator muscle.

Fig. 8: Case 26. Male, white, right side. Three branches are evident here. Two of these, *c* and *c'*, arise from the posterior branch of the obturator nerve, one near the internal orifice of the subpubic canal, and the other near to the external orifice; both pass through this foramen and run along the anterior aspect of the capsule for a certain distance before penetrating it. The third branch, *a.m.*, arises at a high level from the trunk of the obturator nerve; it reaches the canal, perforates its inferior wall, and gives off an acetabular filament, *a*, and another, *m*, to the external obturator muscle.

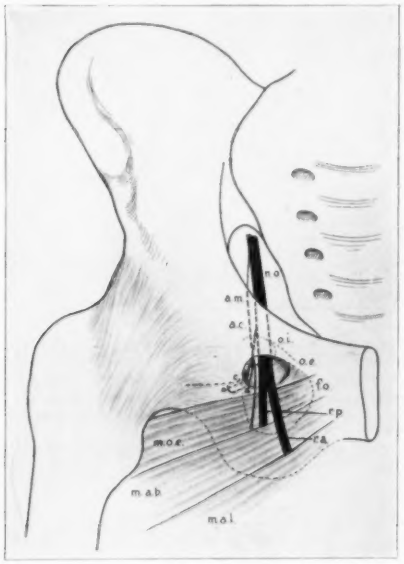

FIG. 9

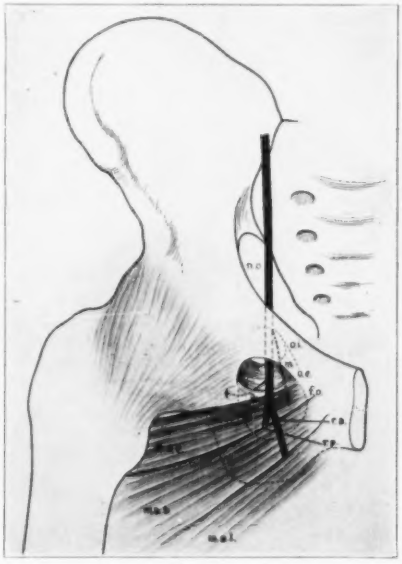

FIG. 10

Fig. 9: Case 53. There are two articular branches: the first, *a.c.*, arises near the internal orifice of the obturator canal, traverses the latter, and bifurcates close to its external orifice into an acetabular filament; *a*, and a capsular filament, *c*. Another branch, *a.m.*, arises within the pelvis and gives off acetabular filaments, *a*, and muscular filaments, *m*. In this joint there are therefore two acetabular branches of different origins.

Fig. 10: Case 14. Male, white, right side. Only an acetabular branch, *a*, is present; it arises from the trunk of the obturator nerve.

In relation to the obturator canal, the origin of the articular branch in the forty-nine specimens was as follows: proximal to the canal, 40.29 per cent.; at the level of its internal orifice, 26.86 per cent.; within the canal, 17.61 per cent.; at the level of its external orifice, 14.92 per cent.

Relation of the Articular Branches of the Obturator Nerve to the Nerve of the External Obturator Muscle

In twenty-two of our forty-nine specimens the articular branches of the obturator nerve and the nerve to the external obturator muscle had a common origin. In six of these twenty-two cases (12.24 per cent. ± 4.6) the capsular, acetabular, and muscular branches had a common origin (Fig. 6); in ten (20.4 per cent. ± 5.8) there was a common origin of the acetabular and muscular branches (Fig. 7), and in six (12.24 per cent. ± 4.6) the capsular and muscular branches had a common origin.

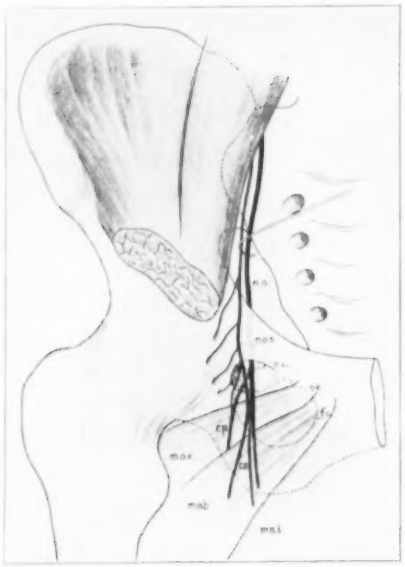

FIG. 11

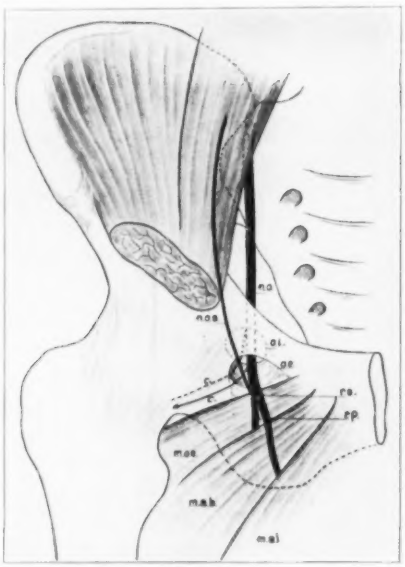

FIG. 12

Fig. 11: Case 28. Male, negro, right side. The suprapubic segment of the accessory obturator nerve gives off four filaments to the articular capsule.

Fig. 12: Case 39. Male, white, right side. There are no articular branches from the accessory obturator nerve. On the other hand, the trunk of the obturator nerve gives off two twigs, one of which perforates the lateral wall of the canal, while the other leaves through the external orifice before penetrating the capsule.

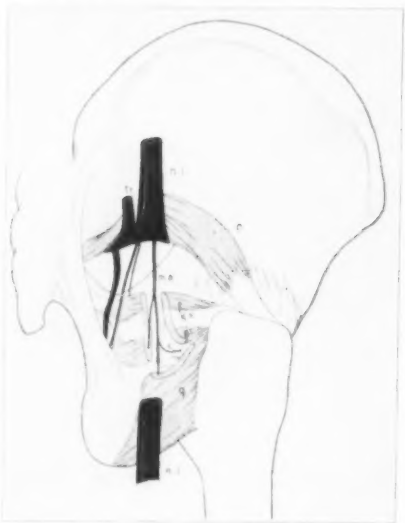

FIG. 13

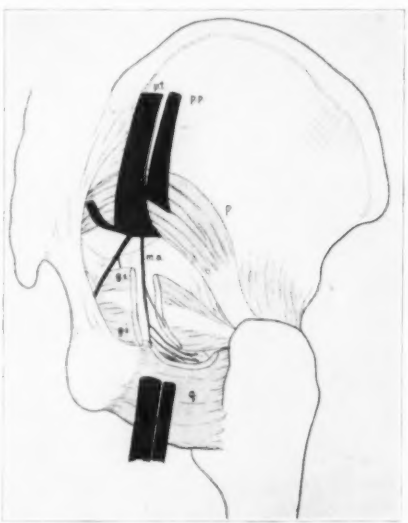

FIG. 14

Fig. 13: Case 9. Male, mulatto, right side. The musculo-articularis nerve, *m.a.*, arises proximal to the inferior border of the foramen ischiaticus major and runs straight down, giving off one twig to the musculus gemellus inferior and another to the capsule before ending in the musculus quadratus femoris.

Fig. 14: Case 5. Right side. This is a case of high division of the ischiatic nerve. The musculo-articularis nerve, *m.a.*, arises from the tibial portion, *p.t.*, above the inferior border of the foramen ischiaticus major; gives off a filament to the musculus gemellus inferior and two to the capsule, ending in the musculus quadratus femoris.

FIG. 15

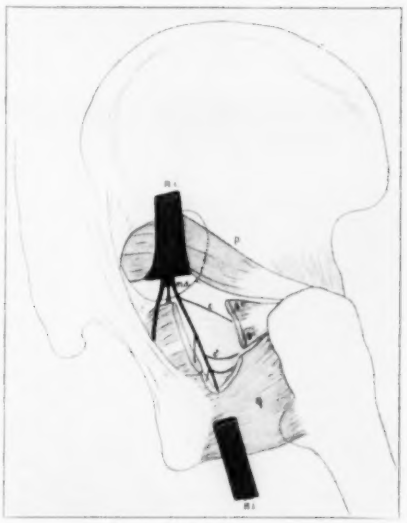

FIG. 16

Fig. 15: Case 23. Male, white, right side. The musculo-articularis nerve, *m.a.*, arises at a point distal to the inferior border of the foramen ischiaticus major, and crosses the superior border of the musculus gemellus superior laterally; thus it may be visualized without a displacement of the sciatic nerve. In its course, it gives off twigs to the gemellus superior, inferior, and quadratus femoris muscles, besides three to the capsule.

Fig. 16: Case 24. Male, mulatto, right side. The musculo-articularis nerve has a common origin with the nerve to the gemellus superior and internal obturator muscles, at the level of the inferior border of the foramen ischiaticus major. It gives off a capsular filament, the branches to the gemellus inferior and quadratus femoris muscles, and two other twigs to the capsule.

Accessory Obturator Nerve

The ventral aspect of the coxofemoral capsule was supplied by this nerve in one case (Fig. 11), in which the obturator nerve did not contribute an articular branch. In another specimen with an accessory obturator nerve, no articular branches from the latter were found; the capsule was innervated by the obturator nerve (Fig. 12).

Femoral Nerve

In twenty-three special preparations of this nerve, no direct branches from the femoral nerve or from its branches to the capsule were found. In seventeen of these preparations there was a twig to the neighboring blood vessels, and in four others there was a twig either to the corresponding muscle or to the periosteum of the pubis. The fineness of the twig made it necessary to do the dissection under a binocular microscope; in only two cases was it large enough to be seen coursing along the vascular adventitia and penetrating the capsule together with the vessel (it originated from the nerve to the pectinaeus muscle in one case and from the nerve to the rectus femoris in the other). The twig to the femoral circumflex vessels was a branch of the nerve to the pectinaeus muscle in thirteen cases (with the participation of another muscular branch of the femoral nerve in five preparations); in the other four cases the twigs to those vessels originated from the nerves to the vasti and rectus femoris muscles in various combinations.

Sacral Plexus

The nerve supply to the dorsal aspect of the capsule of the hip joint was studied in fifty-three specimens, in all of which articular branches were given off by the nerve

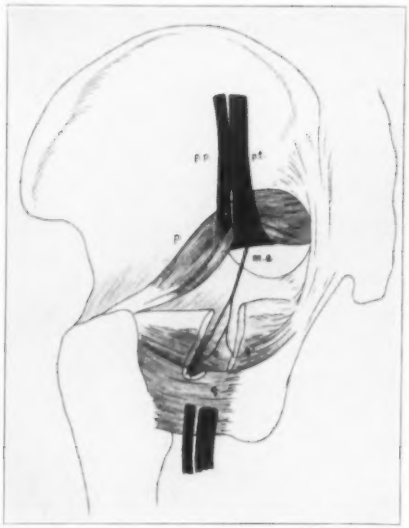

FIG. 17

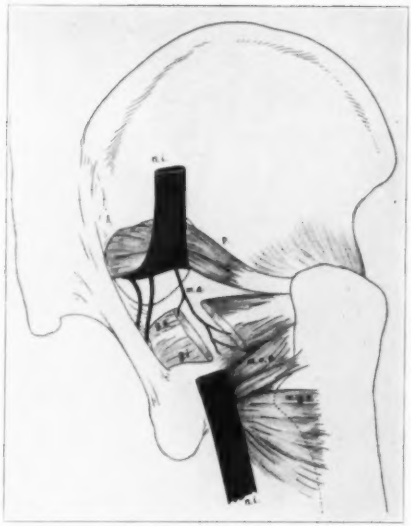

FIG. 18

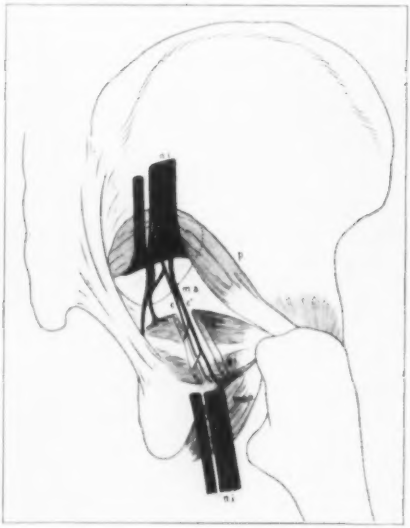

FIG. 19

Fig. 17: Case 12. Male, negro, left side. Shows high division of the sciatic nerve. The musculo-articularis nerve arises from the tibial portion, proximal to the inferior border of the foramen ischiaticus major. The capsular branch, *c*, arises from the nerve to the gemellus inferior. The musculus gemellus superior is missing in this case.

Fig. 18: Case 11. Female, white, right side. The musculo-articularis nerve arises above the inferior outline of the foramen ischiaticus major. After giving off the filaments to the gemellus superior and inferior muscles, it bifurcates and ends in the capsule. There is absence of the musculus quadratus femoris and hypertrophy of the external obturator and adductor magnus muscles.

Fig. 19: Case 18. Male, negro, right side. The musculo-articularis nerve, *m.a.*, arises from two roots above the inferior border of the foramen ischiaticus major and gives off a large branch which goes directly to the articular capsule; the other branch, running parallel to the first, innervates the gemellus superior and inferior muscles and finally terminates in the capsule. Note absence of the musculus quadratus femoris and hypertrophy of the musculus obturator externus.

to the quadratus femoris; in two cases there was an additional direct articular branch from the sciatic nerve.

The nerve to the quadratus femoris and gemellus inferior supplies not only these two muscles but also supplies the articular capsule and occasionally the gemellus superior. For this reason it would be more appropriate to name it "nervus musculo-articularis of the sacral plexus", in spite of the fact that it may be a branch of the sciatic nerve in some 25 per cent. of cases. In fact, the nervus musculo-articularis originated from the sacral plexus in 69.81 per cent. of our cases; from the proximal segment of the sciatic nerve in 24.52 per cent.; and from the tibial part of the sciatic nerve, when the latter presented a high division, in 5.66 per cent. (Figs. 14 and 17). As landmarks for the surgical approach to the nervus musculo-articularis, the following might be used:

TABLE I

ORIGIN OF THE ARTICULAR BRANCHES IN RELATION TO THE TRUNK AND BRANCHES OF THE OBTURATOR NERVE IN FORTY-NINE CASES

No. of Twigs	Origin	No. of Cases
One twig (thirty-three cases)	From the trunk	29
	From the posterior branch	4
Two twigs (fourteen cases)	Both from the trunk	7
	Both from the posterior branch	4
	From trunk and posterior branch	2
	From anterior and posterior branches	1
Three twigs (two cases)	Two from the posterior branch and one from the trunk	1
	Two from the trunk and one from the anterior branch	1

1. Distance from Its Origin to the Lateral Margin of the Vertex of the Sacral Plexus or Sciatic Nerve

In fifty-three preparations the origin of the nervus musculo-articularis was found to lie in any point of the transverse diameter of the sciatic nerve or vertex of the plexus, from the medial to the lateral border. This distance averaged 7.8 millimeters; the maximum was 15 millimeters.

2. Distance from Its Origin to the Inferior Outline of the Foramen Ischiaticus Major

In twenty specimens the origin of the nervus musculo-articularis was proximal to the inferior border of the foramen ischiaticus major (37.73 per cent ± 2.4) (Fig. 13); in sixteen cases the origin was at the level of this border (30.18 per cent ± 6.3), and in seventeen distal to it (32.07 per cent ± 6.4) (Fig. 15). The maximum distance from the origin of the nerve to the inferior border of the foramen ischiaticus major, whether proximal or distal, was 25 millimeters.

The articular nerve may arise directly from the musculo-articular nerve proximal or

TABLE II

ORIGIN OF THE ARTICULAR BRANCHES IN RELATION TO THE OBTURATOR CANAL

No. of Twigs	Origin	No. of Cases
One twig (thirty-three cases)	Proximal to the obturator canal	17
	Level of the internal orifice	7
	Within the canal	6
	Level of the external orifice	3
Two twigs (fourteen cases)	Both within the canal, but from different levels	7
	One proximal to and the other at the level of or distal to the internal orifice	7
Three twigs (two cases)	One proximal and two distal to the internal orifice	1
	Three branches proximal to the internal orifice	1

distal to the origin from the branch to the gemellus inferior muscle (Fig. 16), and occasionally, when the quadratus femoris muscle is not present, it ends as an articular branch (Figs. 18 and 19).

The portion of the nervus musculo-articularis that offers itself most readily to the surgeon is the one between the origin and the upper border of the musculus gemellus superior, for which the term "surgical segment" is proposed. Its maximum length was 45 millimeters and its minimum length 3 millimeters.

CONCLUSIONS

Nerve Supply to the Ventral Aspect of the Hip Joint

1. The articular branch of the obturator nerve to the ventral aspect of the coxofemoral joint is almost constant (98 per cent. ± 2).

2. The articular branches arise more frequently from the trunk of the obturator nerve (71.64 per cent. of the cases ± 6.4) than from either the posterior (23.37 per cent. ± 6.2) or the anterior branch (2.98 per cent. ± 2.4) of the obturator nerve.

3. The articular branch of the obturator nerve is single in 67.34 per cent. ± 6.7 of the cases; in 28.57 per cent. ± 6.4 there are two articular branches, and in 4.08 per cent. ± 2.8 there are three.

4. The articular nerves may be of two types,—that is, capsular (penetrating the capsule), and acetabular (penetrating the incisure of the acetabulum).

5. The capsular branch is present in 93.87 per cent. of the cases; it was missing in only three of our specimens; only the acetabular branch was present in these.

The acetabular branch is present in 59.18 per cent. ± 6.9 of the cases. It arises directly from the trunk or from the terminal branches of the obturator nerve in 14.28 per cent. ± 4.9 of the cases; from the nerve to the external obturator muscle in 18.36 per cent. ± 5.5; from the capsular branch in 26.53 per cent. ± 6.2.

6. A common origin of branches from the obturator nerve was found as follows: articular branch and nerve to the external obturator muscle, in 44.98 per cent. ± 7.1 of the cases; capsular, acetabular, and muscular branches, in 12.24 per cent. ± 4.6; acetabular and muscular branches, in 20.4 per cent. ± 5.8; capsular and muscular branches, in 12.24 per cent. ± 4.6.

7. The origin of the articular branches of the obturator nerve is proximal to the obturator canal (that is, in the pelvic cavity) in 40.29 per cent. ± 7; at the level of the internal orifice of that canal, in 26.86 per cent. ± 6.3; within the canal, in 17.61 per cent. ± 5.4; at the level of its external orifice, in 14.42 per cent. ± 5.1.

8. When present, the accessory obturator nerve may or may not give off filaments to the coxofemoral joint. It was present in two of our specimens and contributed to the innervation of the joint in one case.

9. No direct articular branches from the femoral nerve were found. There are, however, nerve filaments arising from the nerve to the pectinaeus muscle, which follow the medial circumflex vessels, as well as twigs from the nerves to the vastus lateralis, intermedius, medial, and rectus femoris muscles, which follow the lateral femoral circumflex vessels.

Innervation of the Dorsal Aspect of the Hip Joint

1. The dorsal aspect is supplied in all cases by one or more branches arising from the nerve to the musculus quadratus femoris and musculus gemellus inferior. We suggest for the latter the name "nervus musculo-articularis of the sacral plexus". In only two instances was there a concomitant branch directly from the sciatic nerve.

2. The nervus musculo-articularis originates most frequently from the sacral plexus (69.81 per cent. ± 6.3); next most frequently from the initial portion of the sciatic nerve (24.52 per cent. ± 5.9); or from the tibial branch of the sciatic nerve (5.66 per cent. ± 3.2), in cases of high division of the latter.

3. The nervus musculo-articularis arises from the anterior aspect of the transitional segment between the sacral plexus and the sciatic nerve, at a point in the transverse plane somewhere between the lateral and the medial margin.

4. The origin of the nervus musculo-articularis occurs most frequently proximal to the interior outline of the ischiatic foramen (37.73 per cent. ± 2.4); at its level, in 30.18 per cent. ± 6.3; distal to it, in 32.07 per cent. ± 6.4. The maximum distance between this origin (either proximal or distal) and the inferior outline of the ischiatic foramen was 25 millimeters.

5. The initial segment of the nervus musculo-articularis, from its origin down to the upper margin of the musculus gemellus superior, is the part most accessible to the surgeon and might be called its "surgical segment". It may measure between 3 and 45 millimeters in length.

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INSTRUMENT FOR PERFORATING THE GLENOID LIP IN THE BANKART OPERATION

BY PAUL V. HUTCHINSON, M.D., PITTSBURGH, PENNSYLVANIA

With the cooperation of the Sarah Mellon Scaife Foundation's Multiple Fellowship on Orthopaedic Appliances, Mellon Institute, Pittsburgh, Pennsylvania

Many types of drills and instruments have been devised for the perforation of the glenoid lip. The instrument herein described was constructed by modifying an Oneida No. 1 uterine forceps. It has reduced operating time in the Bankart operation by about 35 per cent. The forceps were formed to the desired contour, and the tips were ground to the design of the point of a hand-sewing awl needle (Fig. 1). When the forceps are closed, the points overlap, closely resembling in form a diamond-shaped Steinmann pin. Although various methods of constructing the cutting tips were tried, the form described was found most suitable for this procedure.

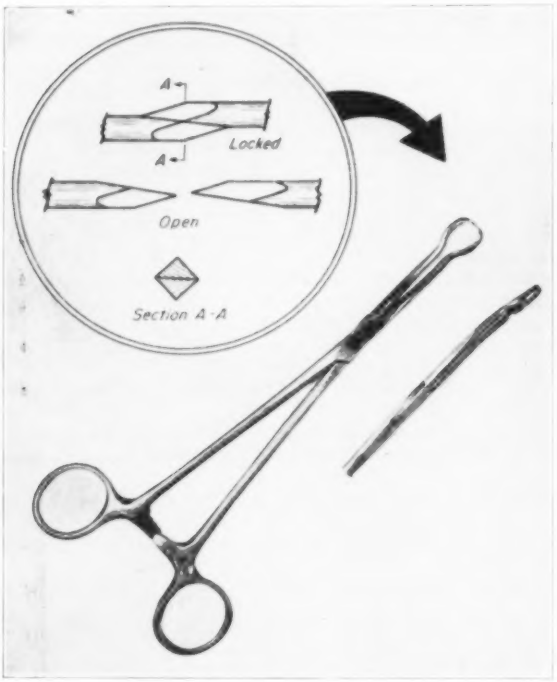

FIG. 1

The glenoid lip is grasped with the tool, and a hole is opened by oscillating the tool in a plane perpendicular to the point. The hole is then enlarged by rotating the locked points through it, back and forth. After the hole has been prepared in this manner, the suture is inserted by use of a reversed, half-curved needle.

A SIMPLE FLEXIBLE SHAFT DRILL ATTACHMENT FOR THE LUCK BONE SAW

BY R. W. COONRAD, M.D., DURHAM, NORTH CAROLINA*
AND C. E. IRWIN, M.D., WARM SPRINGS, GEORGIA

A simple but efficient flexible shaft drill attachment has been devised for the Luck bone saw. This attachment has overcome the difficulty one experiences with the more cumbersome electric drills requiring the use of two hands or with the slower and less accurate hand-operated drills of various types, when inserting short Kirschner wires for the

* Aided by a fellowship from the National Foundation for Infantile Paralysis, Inc., New York, N. Y.

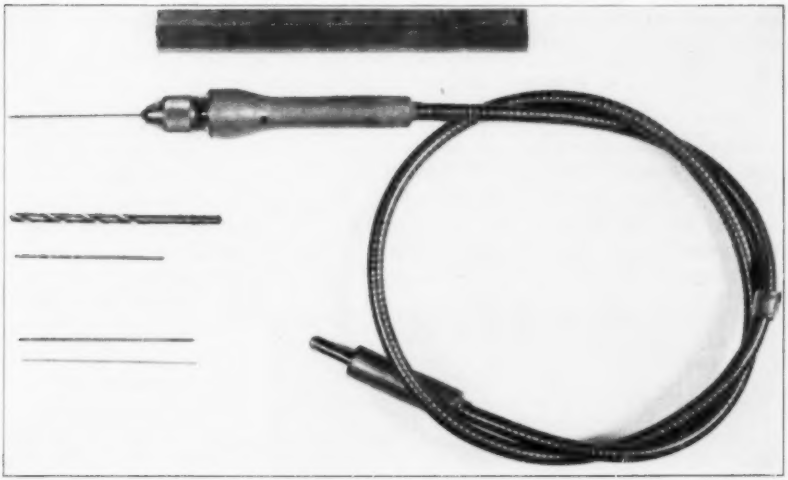

FIG. 1

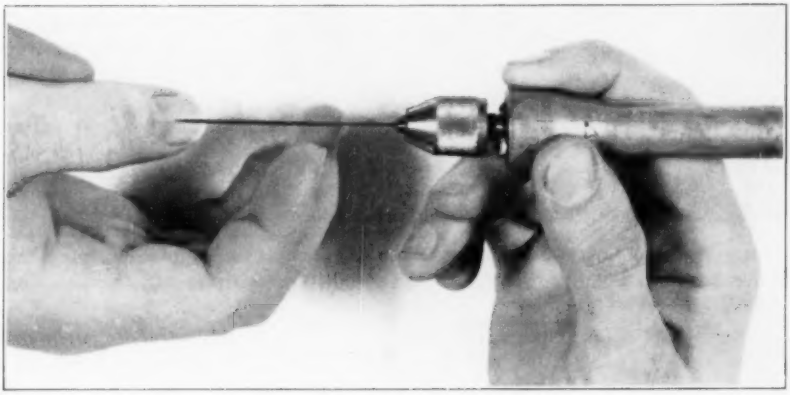

FIG. 2

internal fixation of arthrodeses of the smaller joints of the hands. The attachment can be held and accurately directed with one hand. This allows the operator not only to retain the rotatory speed of electric drills for the ease of insertion into bone, but also to have a free hand with which to help his assistant maintain the accurate position of bony fragments. This attachment has a pen-sized hand piece, which can be easily held with two fingers. Because of its small-caliber, flexible shaft, it can be easily manoeuvered. When it is used with an ordinary drill tip, its size and flexibility eliminate the possibility of breaking drill points,—an accident which often results from the bulk and weight of the conventional electric drills.

The attachment uses a modified Jacobs type hand-operated chuck without a key, which allows for a rapid change in the size of Kirschner wires or drill tips from zero to one-eighth of an inch. The attachment is easily fitted to the Luck bone saw or, for that matter, to any available motor, which may be placed unsupported on a Mayo stand or on a nearby table. The flexible drill shaft attachment has the further advantage of being inexpensive—it can be obtained at a cost of less than five dollars.

SURGICAL APPROACH FOR NEUROMA OF PLANTAR DIGITAL NERVE (MORTON'S METATARSALGIA)

BY DUNCAN C. McKEEVER, M.D., HOUSTON, TEXAS

Two recent articles[2,4] on Morton's metatarsalgia have described and illustrated the removal of neuromata through incisions made in the plantar surface of the foot. Another recent article[1] has depicted a transverse incision under the toes as part of an approach to this area. By instinct and training, the author has an aversion to making an unnecessary incision in the plantar surface of the foot. The beauty of the anatomical demonstration possible through such an incision, extolled as one of its advantages, hardly justifies its use. Such anatomical demonstrations had better be made on cadavera.

FIG. 1

Showing a Morton's neuroma between the metatarsal heads.

In 1941 the writer made an incision in the dorsum of the foot between the third and fourth toes for removal of portions of the bases of the proximal phalanges and heads of the metatarsals in order to relieve the pain in Morton's syndrome. Accidental pressure on the sole of the foot, with the metatarsal heads separated, caused a large mass to present itself between them. This seemed to contain a neuroma and was therefore excised; no other procedures were undertaken. Some weeks later the same operation was performed on the other foot. This also gave complete relief. Since then the author has done the operation seventy-three times.

The skin incision need not be more than one inch in length. Blunt dissection between the metatarsal heads can be made easily with a hemostat. The metatarsal heads can then be separated with two rake retractors, and pressure on the sole of the foot will present the neuroma, or neuromata, in the space between the metatarsal heads where it can be grasped with a hemostat, cut loose at both ends, and removed (Fig. 1). The entire procedure, including the closure, takes less than five minutes. To the present time it has not resulted in failure. The disability is of short duration, and the patient can begin to walk on the same day or the day following.

Until recently the author believed that this was the method in general use. McElvenny reported a similar incision in the web between the toes. Since this neuroma can be removed so simply by a method which entails such a short convalescence, there would seem to be no need for its removal through a plantar incision.

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THE INCIDENCE OF SEPARATE NEURAL ARCH AND COINCIDENT BONE VARIATIONS

A Summary *

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A detailed survey of the lumbosacral vertebrae of 4,200 skeletons was made in order to determine the incidence of the separate neural arch as well as the coincidental appearance of certain specific congenital or acquired characteristics. The study was confined largely to the lumbar vertebrae and was extended to the rest of the column only when a lumbar vertebra was found to present a separation through the pars interarticularis of the neural arch.

All columns presenting isthmal defects were subjected to additional examination for the following characteristics: articular facets for cervical ribs on the seventh cervical vertebra, spina bifida, articulations of the transverse processes of the fifth lumbar vertebra with the sacrum or ilium or both, arthritis of the central atlanto-epistrophic joint, arthritis of the articular processes of the lumbar vertebrae, and certain anatomical variations in the sacrum, including accessory sacro-iliac articulations, incomplete fusion of the first sacral segment, spina bifida of the upper sacral segments, complete spina bifida or open dorsal bony wall of the sacral canal, and rudimentary sacral articular processes; the total number of presacral vertebrae was also recorded. The various arthritic manifestations studied were grouped into classifications of mild, moderate, and severe. This was done by the arbitrary method of gross examination of the articular processes for evidence of wear, deformity, and spurring.

Of the 4,200 skeletons accepted for this study, 178 columns showed isthmal defects, yielding an over-all incidence of 4.2 per cent. However, when the incidence is computed on the basis of ethnic group and sex, it is found to yield significant variations: white male skeletons, 6.4 per cent.; Negro male skeletons, 2.8 per cent.; white female skeletons, 2.3 per cent.; and Negro female skeletons, 1.1 per cent. The incidence of the neural-arch defects remained essentially unchanged within each group for each decade after twenty and up to eighty years of age. Statistical analysis (*Chi* square) revealed no significant difference in incidence between the group aged forty-nine years and under and that aged fifty years and over. The incidence of the separate neural arch is therefore found to remain almost constant regardless of age in those age periods—that is, within the span of adult life—represented by this skeletal material.

As noted, the number of columns showing neural-arch defects was 178. In five of these columns there was more than one separate neural arch, making the total number of separate neural arches 183. In these multiple lesions both separations were bilateral in three cases and a bilateral separation was combined with a unilateral separation in two cases. While the case cited by Friberg had the greatest number of involved vertebrae in a single individual found in the literature, by far the most frequent occurrence of multiple involvements was found by Stewart in Eskimo skeletons.

The defect appeared in a wide variety of patterns not only as regards morphology but in extent of separation as well. The lesion ranged from a narrow unilateral defect in continuity which was no more than a line through the bone (Fig. 1) to a wide bilateral defect in which nothing that could be considered isthmus was present (Fig. 2). In some cases, the defect extended through what appeared to have been a normal isthmus (Fig. 3), but in others the involved isthmus was very thin and appeared to have been weak. In all cases the adjacent ends of the fragments were examined for smoothness, so that no chance of confusion with a post-mortem fracture existed. In addition to defects classified as neural-arch separations there were instances of accompanying separations through the spinous process or through the lamina.

Thirty-two or more than one-sixth of the 183 neural-arch separations were unilateral. These were twice as frequent on the right as on the left side. Unilateral separations constituted 6.7 per cent. of the total separations found in Negroes and 21 per cent. of those found in whites. Regarding sex incidence, 7.2 per cent. of the separations in females were unilateral as compared with 18.3 per cent. in the males. A recurring characteristic with regard to the unilateral separations was the twisted appearance of the neural arch of the involved vertebra (Fig. 4). In almost all unilateral separations encountered the arch was asymmetrical, apparently because of the difference in length between the two isthmi. Hence those with wide separations were more asymmetrical than those with narrow separations.

Bilateral neural-arch separations were found in 3.6 per cent. of the total number of skeletons observed, and constituted five-sixths of the total separations. Of the total separations found in Negroes, 93.3 per cent. were bilateral, as were 79.0 per cent. of those in whites. If division into ethnic groups is disregarded, 92.8 per

* At the request of the Editor, this summary has been made of the complete paper published in the Anatomical Record, 109:233–252, 1951.

FIG. 1

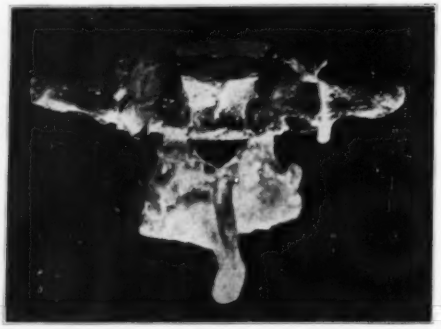

FIG. 2

Fig. 1: Specimen No. 1445. Fifth lumbar vertebra from a Negro male eighty years old. There is a unilateral line defect on the right side.

Fig. 2: Specimen No. 278. Fifth lumbar vertebra from a white male fifty years old. There is a wide defect bilaterally, with absence of isthmi.

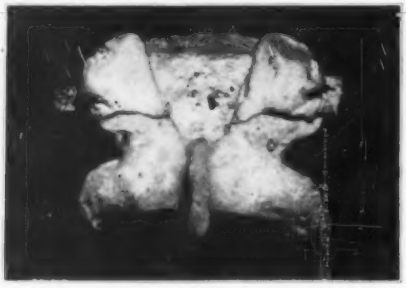

FIG. 3

FIG. 4

Fig. 3: Specimen from a Negro male forty years old. Bilateral line defect. (Lent through courtesy of Dr. J. E. Markee, Department of Anatomy, Duke University School of Medicine, Durham, North Carolina.)

Fig. 4: Specimen No. 320. Fifth lumbar vertebra from a white male forty-three years old. There is elongation of the defective isthmus (left side) with twisted appearance of the neural arch: note the associated cleft spinous process.

cent. of the separations in females and 81.6 per cent. of those in males were bilateral. No significant difference could be demonstrated between the ages of those with bilateral separations and those with unilateral separations.

The present observations confirm the clinical impression that the majority of isthmal separations occur in the fourth and fifth lumbar vertebrae. Of the total number of defects, 94.6 per cent. occurred in these two segments. The first lumbar vertebra presented no separations; there were three in the second lumbar vertebra, five in the third, seventeen in the fourth, 156 in the fifth, and two in the sixth lumbar vertebra within the total of 183 isthmal defects.

As regards ethnic derivation, the incidence is highest in Mongols, next highest in whites, and lowest in Negroes [3, 7, 8, 13, 14, 16, 23].

Coincident Bone Variations

In the light of the known association of several congenital variations in the same individual [3, 6, 20, 21, 22] it seemed appropriate to search the vertebral columns which presented a separate neural arch for the presence of certain other bone variations, and when possible to compare the incidence of these coincident variations with the incidence already established in unselected groups of skeletons.

Number of presacral segments: Upon such a basis, there seems to be no significant difference between the incidence of 2.5 per cent. with twenty-three presacral segments, 92.5 per cent. with twenty-four, 5.0 per cent. with twenty-five presacral segments in the present series and the incidence found by Lanier. These findings also correspond closely with those in Bardeen's summary of the literature.

Articular facets for cervical ribs and *spina bifida of the cervical vertebrae* had an incidence which compared favorably with that found in unselected groups by Lanier and Todd.

Spina bifida of the fifth lumbar vertebra was combined with neural-arch separation in nine cases, or 5.9 per cent. of the 153 satisfactory specimens. (The total number of satisfactory specimens for this examination is somewhat lower than most in this series because of the frequent loss of the separated segment.) This incidence is about ten times the expected rate as determined by Lanier for the fifth lumbar vertebra on the basis of examination of 100 white and 100 Negro male skeletons. It is four and one-half times the frequency determined by Willis [24] for the last lumbar vertebra in 748 lumbo-sacral columns unselected as to ethnic group and sex. The lumbar vertebrae other than the fifth presented no spina bifida except for the two cases of bilateral separation through the sixth lumbar vertebra; in both of these the separated fragment was bisected by a central separation, so that both were cases of spina bifida.

Enlarged transverse processes of the fifth lumbar vertebra were found to articulate with the sacrum or ilium or both in three of 171 cases satisfactory for examination or in 1.8 per cent. Similar articulations were reported by Moore to occur in 6 per cent. of unselected skeletons and by Lanier to occur in 6 per cent. of white males and 8.0 per cent. of Negro males, or approximately three to four times as frequently.

Spina bifida of the first sacral segment was found in thirty or 17.4 per cent. of 172 sacra satisfactory for examination. This is essentially the same as that reported by Adolphi. Of the thirty sacra in this series with spina bifida of the first sacral segment, the posterior wall of the sacral canal was open throughout in seven cases, or 4.1 per cent. of the total number of sacra. This incidence of the open type of sacrum is approximately twice as frequent as that found by Trotter [18] in unselected groups of bones. The fact that such a defect in the dorsal sacral wall is twice as frequent in association with neural-arch defects is of significance to surgeons approaching this level for purposes of spine fusion.

Other sacral variations: Accessory sacro-iliac articulations were observed in 15.7 per cent., as compared with the previously established incidence of 50.5 per cent. in white and 20.7 per cent. in Negro skeletons selected at random by Trotter [18]. Incomplete fusion of the first with the second sacral segment was present in seven, or 4.1 per cent., of these sacra. A rudimentary superior articular process of the first sacral segment was demonstrated in four, or 2.3 per cent. of the 172 sacra in this group.

Arthritis of articular processes of the lumbar vertebrae: It was thought that, if chronic trauma plays any significant role in the etiology of the separate neural arch, perhaps in those columns in which the separations occurred there might be found a greater degree of hypertrophic or traumatic arthritic changes, at least at the level at which the defects occurred. Of those columns with a neural-arch defect, 32.4 per cent. presented some arthritic involvement of the lumbar facets and 67.6 per cent. were grossly normal. Breakdown of these by age revealed that only one case of arthritis, and that one of mild degree, occurred before the age of forty, and that subsequently there was an increase in the frequency and severity of the arthritic manifestations with increase in age. Our findings correspond closely to those of Shore [15] and Putti and Logroscino in unselected material. When involvement of the cervical joints was studied, arthritic manifestations were found to be almost twice as frequent in that area as in the region of the column presenting a neural-arch separation.

Summary

1. A differential analysis of factors related to the separate neural arch includes incidence in relation to age, ethnic group, and sex.

2. In a group of 4,200, there were 178 skeletons which presented neural-arch separations, establishing an over-all incidence of 4.2 per cent. On the basis of ethnic group and sex, the incidence is as follows: white males, 6.4 per cent.; Negro males, 2.8 per cent.; white females, 2.3 per cent.; and Negro females, 1.1 per cent.

3. The frequency of occurrence of the separate neural arch is shown to remain almost constant regardless of age in those age periods (adult life) represented by this skeletal material.

4. In this series of columns with isthmal separations the coincident bone variations which had an incidence significantly different from determination in the normal were as follows: Spina bifida of the fifth lumbar vertebra was approximately four and one-half times as frequent as is normally expected; the open sacrum was approximately twice as frequent; articulation of the transverse process of the fifth lumbar vertebra was approximately one-third as frequent; accessory sacro-iliac articulations were approximately one-half as frequent.

5. Those coincident bone variations studied in this series which had an incidence essentially the same as that found in unselected bones were as follows: atypical number of presacral vertebrae, cervical ribs, spina bifida of vertebrae other than the fifth lumbar, spina bifida of the upper sacral segments.

6. Arthritic involvement of the lumbar vertebral articular processes increased in frequency and severity with increasing age, but was absent to gross inspection in over two-thirds of those columns showing isthmal separations.

Note: Grateful acknowledgment is made to Dr. Mildred Trotter for continued help and encouragement in preparation of the manuscript.

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DISCUSSION

Congenital Kyphoscoliotic Tibia

(*Continued from page 371*)

It is quite possible that the underlying condition producing the series of events may be based on a fault in the invasion of the neurovascular elements from the trunk; this may be due to intrinsic hereditary factors or to environmental factors such as vitamin deficiencies or infections occurring early in pregnancy.

The aim of treatment should be protection from fracture, either by corrective measures or by operative procedures. Spontaneous correction can occur in this condition.

News Notes

THE AMERICAN ORTHOPAEDIC ASSOCIATION

The Sixty-fifth Annual Meeting of The American Orthopaedic Association, under the presidency of Dr. Fremont A. Chandler, will be held in London, England, on June 30, July 1, 2, 3, and 4. The meeting will be held jointly with the Orthopaedic Associations of the British Commonwealth, including The British Orthopaedic Association, the Canadian Orthopaedic Association, the Australian Orthopaedic Association, the New Zealand Orthopaedic Association, and the South African Orthopaedic Association.

The organizing committee of The British Orthopaedic Association, under the presidency of Sir Reginald Watson-Jones, has arranged an unusually interesting program. The Scientific Meetings will be held in the Senate House of the University of London with presentation of papers from the various Orthopaedic Associations. The meetings will be held in the morning and afternoon on June 30 and thereafter in the mornings only. Ample opportunity will thus be given for sightseeing and for visiting clinics in London and its environs. An attractive program of social events has been planned by the Committee.

The tentative program of the meeting, as submitted by the Program Committees, is as follows:

The American Orthopaedic Association

Arthroplasty for Congenital Dislocation of the Hip.
Paul C. Colonna, M.D., Philadelphia, Pennsylvania.
Ischaemic Hand.
Sterling Bunnell, M.D., San Francisco, California.
Selection of the Fusion Area for Scoliosis.
John R. Cobb, M.D., New York, N. Y.
Care of Osseous and Joint Tuberculosis.
David M. Bosworth, M.D., New York, N. Y.
Surgical Management of the Arthritic Hip.
Frank Stinchfield, M.D., New York, N. Y.
The Treatment of Fracture-Dislocation of the Cervical Spine.
William A. Rogers, M.D., Boston, Massachusetts.
Orthopaedic Operation and Stress Reaction.
Philip Wilson, M.D., New York, N. Y.
Neurofibromatosis and Orthopaedics.
H. R. McCarroll, M.D., St. Louis, Missouri.
Filum Terminale Syndrome.
George Garceau, M.D., Indianapolis, Indiana.
Pathological Gait.
Verne T. Inman, M.D., San Francisco, California.
Major Determinants of Normal Gait.
John B. deC. M. Saunders, M.D., San Francisco, California.
Dislocation and Fracture-Dislocation of the Hip.
J. Spencer Speed, M.D., and Marcus J. Stewart, M.D., Memphis, Tennessee.
The Care of Crippled Children in the United States.
A. R. Shands, M.D., Wilmington, Delaware.

The British Orthopaedic Association

Forty-eight Cases of Causalgia.
R. Barnes, Glasgow, Scotland.
Some Experiences in the Evolution of a New Operation for Osteo-Arthritis of the Hip.
J. Charnley, Manchester.
The Diagnosis of Shoulder-Cuff Lesions Due to Injuries of the Rotator Cuff.
V. H. Ellis, London.
Bone Changes in Leukaemia.
D. Ll. Griffiths, Manchester.
Treatment of Traumatic Paraplegia.
F. Holdsworth, Sheffield.
Idiopathic Scoliosis: Diagnosis, Prognosis, and Operative Indications Related to Curve Patterns.
J. I. P. James, Hemel Hempstead, England.
Traumatic Dislocation of the Hip.
E. A. Nicoll, Mansfield.

The Etiology of Carpal Tunnel Compression of the Median Nerve.
K. I. Nissen, Stanmore.
Congenital Phalangeal Fusion through Nineteen Generations.
I. Patterson.
Ulnar Neuritis from Ganglion Pressure.
H. J. Seddon, London.
Man with Three Legs.
I. Smillie, Dundee, Scotland.
Posterior Subtaloid Fusion in the Treatment of Fracture of the Os Calcis.
I. L. Dick, Bradford.
Posterior Peripheral Detachment of the Lateral Meniscus.
E. Jack, Edinburgh, Scotland.
Osteoid Osteoma.
J. Golding.

THE CANADIAN ORTHOPAEDIC ASSOCIATION

Structural Changes in the Lumbosacral Region and Their Significance as Causes of Low-Back Pain and Sciatica.
Ian MacNab and R. I. Harris, Toronto, Ontario.
Results of Patellectomy.
H. H. Boucher, Vancouver, British Columbia.
The Posterolateral Approach in the Treatment of Congenital Dislocation of the Hip Joint.
A. Gibson, Winnipeg, Manitoba.
An Unusual Case of Neurological Arthropathy.
J. Gordon Petrie, Montreal, Quebec.

THE AUSTRALIAN ORTHOPAEDIC ASSOCIATION

Ischiofemoral Arthrodesis with Internal Fixation for Tuberculous Disease of the Hip Joint.
T. King, Melbourne, Victoria.
Spondylolisthesis.
Esmond F. West, Adelaide, South Australia.

AMERICAN MEDICAL ASSOCIATION
SECTION ON ORTHOPAEDIC SURGERY

CHICAGO, ILLINOIS, JUNE 9 TO 13, 1952

OFFICERS OF SECTION

Chairman: Frederic C. Bost, M.D., San Francisco, California
Vice-Chairman: H. Relton McCarroll, M.D., St. Louis, Missouri
Secretary: Charles N. Pease, M.D., Chicago, Illinois
Executive Committee: Joseph S. Barr, M.D., Boston, Massachusetts
Walter P. Blount, M.D., Milwaukee, Wisconsin
Frederic C. Bost, M.D., San Francisco, California

TUESDAY, JUNE 10

2:00 P.M.

Recurring Dislocation of the Shoulder: Operative Treatment. Pertinent Anatomic, Functional, and Pathologic Features.
R. W. Newman, M.D., Iowa City, Iowa.
Discussion to be opened by George L. Dixon, M.D., Tucson, Arizona, and Carlo S. Scuderi, M.D., Chicago, Illinois.

Synovectomy of the Knee Joint: Indications and End Results. A Preliminary Report.
Pio Blanco, M.D., Buffalo, New York.
Discussion to be opened by Clinton L. Compere, M.D., Chicago, Illinois, and William A. Larmon, M.D., Chicago, Illinois.

Tuberculous Tenosynovitis.
William H. Bickel, M.D., Rochester, Minnesota; Robert F. Kimbrough, M.D., Fort Wayne, Indiana; and David C. Dahlin, M.D., Rochester, Minnesota.
Discussion to be opened by Frederick C. Thompson, M.D., New York, and Harvey S. Allen, M.D., Chicago, Illinois.

Paraplegia Resulting from Tuberculosis of the Spine.
David M. Bosworth, M.D., New York, N. Y.; Alphonso Della Pietra, M.D., Hartford, Connecticut; and George Rahilly, M.D., Fort Lauderdale, Florida.
Discussion to be opened by Ignacio Ponseti, M.D., Iowa City, Iowa, and Robert O. Ritter, M.D., Chicago, Illinois.

The Conservative and Prophylactic Surgical Management of Foot Lesions in the Diabetic.
James W. Miller, M.D., Seattle, Washington.
Discussion to be opened by Donald C. Conzett, M.D., Dubuque, Iowa, and Jerome G. Finder, Chicago, Illinois.

The Treatment of Subacute and Chronic Osteomyelitis with the Use of Antibiotics and Primary Closure.
Frank D. Dickson, M. D., Rex L. Diveley, M.D., and Richard H. Kiene, M.D., Kansas City, Missouri.
Discussion to be opened by Theodore H. Vinke, M.D., Cincinnati, Ohio, and Earl S. Leimbacher, Joliet, Illinois.

WEDNESDAY, JUNE 11

2:00 P.M.

Election of Officers

Misdiagnosis and Mismanagement of Early Intervertebral-Disc Lesions.
L. Stanley Sell, M.D., Idaho Falls, Idaho.

Myleography—Use or Abuse.
Frank L. Shipp, M.D., Boston, Massachusetts.
Discussion on papers of Dr. Sell and Dr. Shipp to be opened by Loyal Davis, M.D., Chicago, Illinois; J. Albert Key, M.D., St. Louis, Missouri; and Reed S. Clegg, M.D., Salt Lake City, Utah.

Chairman's Address: Frederic C. Bost, M.D., San Francisco, California

Calcaneovalgus Foot in the Newborn and Its Relation to Developmental Flat-Foot.
C. Fred Ferciot, M.D., and Frederick S. Webster, M.D., Lincoln, Nebraska.
Discussion to be opened by Walter P. Blount, M.D., Milwaukee, Wisconsin, and Albert L. Bershon, M.D., Toledo, Ohio.

Hemangiomata in Orthopaedic Surgery.
James B. Weaver, M.D., Kansas City, Kansas.
Discussion to be opened by J. Vernon Luck, M.D., Los Angeles, California, and Robert D. Moore, M.D., Kankakee, Illinois.

THURSDAY, JUNE 12

2:00 P.M.

Trigger-Point Scapulocostal Syndrome.
Arthur A. Michele, M.D., Brooklyn, New York.
Discussion to be opened by Ruth Jackson, M.D., Dallas, Texas, and Jesse B. Griffith, M.D., Pittsburgh, Pennsylvania.

The Conservative Management of the Fractures of the Ankle Involving the Medial Malleolus.
Robert B. Portis, M.D., and Howard A. Mendelsohn, M.D., Beverly Hills, California.
Discussion to be opened by Fred Stuttle, M.D., Peoria, Illinois, and Alan R. Cantwell, M.D., New York, N. Y.

The Problem of the Muscular Dystrophies.
Robert H. Ramsey, M.D., and H. Relton McCarroll, M.D., St. Louis, Missouri.
Discussion to be opened by W. R. Roberts, M.D., Gastonia, North Carolina, and William J. Schnute, M.D., Chicago, Illinois.

Fracture of the Carpal Scaphoid.
Marcus J. Stewart, M.D., Memphis, Tennessee.
Discussion to be opened by F. W. Carruthers, M.D., Little Rock, Arkansas, and Newton C. Mead, M.D., Evanston, Illinois.

Evaluation of Twenty Successive Unselected Cases of Intramedullary Fixation of Fractures of the Forearm.
R. C. Robertson, M.D., and John J. Killeffer, M.D., Chattanooga, Tennessee.

The Treatment of Certain Fractures of the Forearm with the Küntscher Nail.
J. E. M. Thomson, M.D., Duane A. Willander, M.D., and Edward S. Maxim, M.D., Lincoln, Nebraska.
Discussion on papers of Dr. Robertson and Dr. Killeffer and Dr. Thomson, Dr. Willander, and Dr. Maxim to be opened by Dana Street, M.D., Memphis, Tennessee, and Bruce Brewer, M.D., Milwaukee, Wisconsin.

Dr. Leo Mayer of New York City has been invited to deliver the Moynihan Lecture on July 3 before the Royal College of Surgeons.

Part I Examinations of **The American Board of Orthopaedic Surgery** will be given on April 25 and 26, 1952, in San Francisco, California, and Washington, D. C.

The **Société Grecque de Chirurgie Orthopédique et de Traumatologie** is now five years old. The officers for 1952 are as follows: Chairman, Dr. L. A. Karabarbounis; Vice-President, Dr. Sarantis-Papadopoulos; Secretary, Dr. Ath. Contargyris; Treasurer, Dr. P. Antonopoulos; Assistant Secretary, Dr. Papageorgantas. The address of the Chairman is Rue Loukianou 6, Athens, Greece.

Dr. Robert Judet, as a guest of the Boston City Hospital on February 16, 1952, headed a symposium on the use of his acrylic prosthesis for the femoral head. Boston hospitals were represented in the discussion with reports of cases by Dr. A. A. Thibodeau of the New England Medical Center, Dr. J. J. McGillicuddy of St. Elizabeth's Hospital, Dr. T. A. Potter of the Robert Breck Brigham Hospital, and Dr. C. A. Bradford of the Boston City Hospital. Papers were discussed by Dr. Russell F. Sullivan and Dr. M. N. Smith-Petersen.

The meeting was well attended; enthusiasm was expressed over the remarkably clear and factual presentation of Dr. Judet as well as for his scrupulously objective follow-up studies of more than 600 cases which he has observed for more than five years.

The Hospital for Crippled Children, 89 Park Avenue, Newark, New Jersey, has announced that applications for a residency in orthopaedic surgery from July 1, 1952, to July 1, 1954, are now being considered. Application forms may be obtained from Dr. Harry Merliss, Secretary; application forms are also available for the vacancy on July 1, 1954.

Applications for several one-year residencies in children's orthopaedic surgery at **The Newington Home and Hospital for Crippled Children** are now being considered. Two appointments will be made in July 1952 and two in January 1953. Application forms may be obtained from Dr. Burr H. Curtis, Chairman of the Resident Education Committee, Newington 11, Connecticut.

THE KAPPA DELTA AWARD FOR RESEARCH IN ORTHOPAEDIC SURGERY

A prize of $1,000, donated by the Kappa Delta Sorority, may be awarded annually by The American Academy of Orthopaedic Surgeons for the best research related to orthopaedic surgery performed by an American citizen in the United States of America. The work must be presented to the Committee on Scientific Investigation of The American Academy of Orthopaedic Surgeons before November 1, 1952. Men doing research who are interested in competing for this prize are requested to secure further information from Dr. Claude N. Lambert, Chairman of the Award Committee for 1952, 104 South Michigan Avenue, Chicago 3, Illinois.

1952 ESSAY CONTEST IN PLASTIC AND RECONSTRUCTIVE SURGERY

The Foundation of the American Society of Plastic and Reconstructive Surgery offers Junior and Senior Awards for original contributions in Plastic Surgery.

Junior Award: Two six-month scholarships in leading plastic surgery services in the United States, England, and Italy are given. The contest is open to those plastic surgeons who have been in the specialty not more than five years.

Senior Award: The Foundation's annual prize—the Silver Plaque—is awarded for the best essay presented at the Annual Meeting of the American Society of Plastic and Reconstructive Surgery.

The winning essays in both classifications will appear on the program of the forthcoming Annual Meeting of the American Society of Plastic and Reconstructive Surgery, to be held in New York City in November 1952. All entries must be received by the Award Committee not later than September 1, 1952. For full particulars, write to: The Award Committee, in care of Jacques W. Maliniac, M.D., 11 East 68th Street, New York 21, N. Y.

THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

The American Academy of Orthopaedic Surgeons convened at the Palmer House in Chicago, January 26 to 31, 1952, for the Annual Meeting, under the presidency of Dr. Joseph S. Barr.

Under the chairmanship of Dr. Frank Stinchfield the Audio-Visual Program was well arranged and attracted large interested audiences.

The Instructional Courses under the chairmanship of Dr. Charles N. Pease drew the largest attendance in the history of the Academy. There were seventy-one courses given by a faculty of seventy-four instructors. The Instructional Course Dinner, held in the Grand Ballroom on Monday evening, provided enjoyment and instruction through the "Panel of Experts".

The Program Committee, with Dr. George O. Eaton as chairman, presented an outstanding Scientific Program on Monday afternoon, Tuesday, Wednesday, and Thursday forenoon, as follows:

Monday, January 28

Afternoon Session

Experimental Causation of Congenital Skeletal Defects and Its Significance in Orthopaedic Surgery.
P. K. Duraiswami, M.S., M.Ch. Orth., F.R.C.S., New Delhi, India (by invitation).
Discussion: Charles W. Goff, M.D., Hartford, Connecticut;
Joseph A. Freiberg, M.D., Cincinnati, Ohio.

Osteochondritis in Children.
William T. Green, M.D., Boston, Massachusetts;
Henry H. Banks, M.D., Boston, Massachusetts (by invitation).
Discussion: Charles H. Herndon, M.D., Cleveland, Ohio;
Donald E. King, M.D., San Francisco, California.

Tuesday, January 29

Morning Session

Results of Resection-Reconstruction of the Hip with Acrylic Prosthesis.
Robert Judet, M.D., Paris, France (by invitation);
Jean Judet, M.D., Paris, France (by invitation).

The "Light-Bulb" Type of Prosthesis for the Femoral Head.
J. E. M. Thomson, M.D., Lincoln, Nebraska;
C. F. Ferciot, M.D., Lincoln, Nebraska;
W. W. Bartels, M.D., Lincoln, Nebraska;
Frederick S. Webster, M.D., Lincoln, Nebraska (by invitation).

A Three-Year Report on the Use of the Metallic Femoral Head Prosthesis for Hip Joint.
Earl D. McBride, M.D., Oklahoma City, Oklahoma.

The Minneapolis Intramedullary Femoral-Head Prosthesis.
Richard E. Reiley, M.D., Minneapolis, Minnesota;
Edward T. Evans, M.D., Minneapolis, Minnesota.
Discussion (four papers): Joseph E. Brown, M.D., Cleveland, Ohio;
Harold R. Bohlman, M.D., Baltimore, Maryland;
George J. Garceau, M.D., Indianapolis, Indiana;
Fremont Chandler, M.D., Chicago, Illinois.

An Operative Procedure for Treatment of Dupuytren's Contracture.
H. vH. Thatcher, M.D., Portland, Oregon (by invitation).

Dupuytren's Contracture: Treatment by Subcutaneous Fasciotomy and Excision of Nodules and Plaques.
J. Vernon Luck, M.D., Los Angeles, California.
Discussion (two papers): Joseph H. Boyes, M.D., Los Angeles, California (by invitation);
Walter C. Graham, M.D., Santa Barbara, California;
Michael L. Mason, M.D., Chicago, Illinois (by invitation).

Afternoon Session

The Management of Impacted Fractures of the Neck of the Femur.
George E. Bennett, M.D., Baltimore, Maryland.
Discussion: M. N. Smith-Petersen, Boston, Massachusetts;
J. Albert Key, M.D., St. Louis, Missouri.

Experiences with One Hundred Consecutive Cases of Vitallium-Mold Arthroplasty Performed through the Posterolateral Approach to the Hip Joint.
Paul R. Lipscomb, M.D., Rochester, Minnesota;
J. R. Barber, M.D., Rochester, Minnesota (by invitation);
Discussion: Carroll B. Larson, M.D., Iowa City, Iowa;
Alexander Gibson, M.D., Winnipeg, Canada.

Presidential Address.
Joseph S. Barr, M.D., Boston, Massachusetts.
Studies on Congenitally Dislocated Hips.
Erik Severin, M.D., Goteborg, Sweden (by invitation).
Shelf Operation for Dysplasia of the Acetabulum, Congenital Subluxation, and Luxation of the Hip Joint.
Gunnar Wiberg, M.D., Lund, Sweden (by invitation).

WEDNESDAY, JANUARY 30

Morning Session

Orthopaedic Care of the Wounded in the Far East Command.
Harold Boyd, M.D., Memphis, Tennessee.
Intramedullary Nailing in Selected Gunshot Fractures of the Femoral Shaft.
Col. Ernest A. Bray, Medical Corps, San Francisco, California;
Col. Vinnie H. Jeffress, Medical Corps, San Francisco, California (by invitation).
Experiences with Intramedullary Fixation in Compound War Wounds.
Commander C. R. Carr, Medical Corps, United States Navy, Oakland, California;
Commander Derrick Turnipseed, Medical Corps, United States Navy, Oakland, California (by invitation).
Discussion (two papers): Col. Oral B. Bolibaugh, Medical Corps, San Francisco, California; Col. August W. Spittler, Medical Corps, Washington, D. C. (by invitation).
Closed Reduction, Plate Fixation, and Medullary Nailing of Fractures of Both Bones of the Leg. A Comparative End-Result Study.
J. O. Lottes, M.D., St. Louis, Missouri (by invitation);
L. J. Hill, M.D., St. Louis, Missouri (by invitation);
J. A. Key, M.D., St. Louis, Missouri.
Discussion: S. Benjamin Fowler, M.D., Nashville, Tennessee; Rufus H. Alldredge, M.D., New Orleans, Louisiana.
Multiple Osteotomies and Metal-Rod Fixation for Osteogenesis Imperfecta.
Harold A. Sofield, M.D., Oak Park, Illinois;
Manley A. Page, M.D., Oak Park, Illinois;
Newton C. Mead, M.D., Evanston, Illinois.
Discussion: George K. Carpenter, M.D., Nashville, Tennessee; J. R. Moore, M.D., Philadelphia, Pennsylvania.

Afternoon Session

A Study in the Use of Bank Bone for Spine Fusion in Tuberculosis.
David M. Bosworth, M.D., New York, N. Y.;
J. Wm. Fielding, M.D., New York, N. Y. (by invitation);
E. Raymond Goodrich, M.D., New York, N. Y. (by invitation).
Experimental Study of the Fate of Bone Grafts.
Crawford J. Campbell, M.D., Albany, New York;
Thomas Brower, M.D., Albany, New York (by invitation);
Glen MacFadden, M.D., Albany, New York (by invitation);
Edward Paine, M.D., Albany, New York (by invitation);
James Doherty, M.D., Albany, New York (by invitation).
Discussion (two papers): Robert D. Ray, M.D., Seattle, Washington (by invitation); Fred C. Reynolds, M.D., St. Louis, Missouri.
The Importance of Direct Surgical Attack upon Lesions of the Vertebral Bodies, Particularly in Pott's Disease.
R. W. Johnson, Jr., M.D., Baltimore, Maryland;
J. Wm. Hillman, M.D., Baltimore, Maryland (by invitation);
Wayne O. Southwick, M.D., Baltimore, Maryland (by invitation).
Discussion: Philip H. Moore, M.D., Mt. Edgecumbe, Alaska (by invitation); F. P. Dewar, M.D., Toronto, Ontario (by invitation).
The Use of Manipulation in the Treatment of Painful Back.
Edward G. Ewer, M.D., Oakland, California.
Discussion: C. Leslie Mitchell, M.D., Detroit, Michigan; Mather Cleveland, M.D., New York, N. Y.
Observations on Clothing the Scoliotic Patient.
Henry F. Ulrich, M.D., Baltimore, Maryland.
Discussion: John R. Cobb, M.D., New York, N. Y.; Rex L. Diveley, M.D., Kansas City, Missouri.

THURSDAY, JANUARY 31

Morning Session

Venous Thrombosis as It Applies to Orthopaedic Patients.
Alton Ochsner, M.D., New Orleans, Louisiana;
Paul DeCamp, M.D., New Orleans, Louisiana (by invitation);
Rudolph Landry, M.D., Rochester, Minnesota (by invitation).

A Clinical Evaluation of Tendon Transplantations for Poliomyelitis Affecting the Lower Extremity.
Raymond F. Kuhlmann, M.D., Burlington, Vermont (by invitation);
John F. Bell, M.D., Burlington, Vermont;
Discussion: Thomas Gucker, III, M.D., Warm Springs, Georgia;
Herman W. Wirka, M.D., Madison, Wisconsin.

Cystic Angiomatosis of the Skeletal System.
Julian E. Jacobs, M.D., Charlotte, North Carolina;
Paul Kimmelstiel, M.D., Charlotte, North Carolina (by invitation);
Discussion: Edgar M. Bick, M.D., New York, N. Y.;
Clinton Compere, M.D., Chicago, Illinois.

Subtrochanteric Osteotomy Correction of Slipped Upper Femoral Epiphysis.
Wm. M. Roberts, M.D., Gastonia, North Carolina;
Lieut. Com. Thomas D. Yocum, Medical Corps, United States Navy, Newport, Rhode Island (by invitation).
Discussion: Armin Klein, M.D., Boston, Massachusetts;
J. Hiram Kite, M.D., Atlanta, Georgia.

The first Executive Session was held on Monday afternoon, January 28. The second Executive Session was held at noon on Thursday, January 31. At the first Executive Session, membership certificates were presented to the new members. Following is a list of the newly elected Fellows:

Max Adelman, M.D., Brooklyn, New York
Gerald S. Ahern, M.D., Corpus Christi, Texas
James C. Amspacher, M.D., Oklahoma City, Oklahoma
Joseph J. Amster, M.D., New York, N. Y.
George L. Apfelbach, M.D., Chicago, Illinois
Frank S. Babb, M.D., St. Paul, Minnesota
Dan R. Baker, M.D., Sayre, Pennsylvania
Joseph W. Batch, M.D., Arlington, Virginia
Eugene Frederick Berkman, M.D., Beaver, Pennsylvania
Wm. Henry Blodgett, M.D., Detroit, Michigan
Michael Bluhm, M.D., San Jose, California
Harrison O. Bourkard, M.D., Knoxville, Tennessee
Frank B. Boyle, M.D., Port Arthur, Texas
Chas. Edwin Brighton, M.D., Tulsa, Oklahoma
Thomas F. Broderick, Jr., M.D., Boston, Massachusetts
Robert S. Brua, M.D., San Antonio, Texas
Wesley H. Burnham, M.D., Minneapolis, Minnesota
Leonard F. Bush, M.D., Danville, Pennsylvania
Maurice A. Canon, M.D., Corpus Christi, Texas
John Lidelle Chandler, Jr., M.D., Augusta, Georgia
Peter Cordasco, M.D., Newark, New Jersey
Frederick S. Craig, M.D., New York, N. Y.
William E. Daner, M.D., Richmond, Virginia
Alfonso Della Pietra, M.D., Hartford, Connecticut
Frederick P. Dewar, M.D., Toronto, Ontario, Canada
William Minor Deyerle, M.D., Richmond, Virginia
James Willard Dowell, M.D., Baton Rouge, Louisiana
Kenneth Robert Duff, M.D., Houston, Texas
John Taylor Ealy, M.D., Philadelphia, Pennsylvania
William Bernard Ein, M.D., Newark, New Jersey
David Samson Eisenberg, M.D., Newark, New Jersey
James A. Elkins, M.D., Columbus, Georgia
Wilfred H. Emery, M.D., Glendale, California
Harry E. Emmel, M.D., Seattle, Washington
John J. Euliano, M.D., Erie, Pennsylvania
Aladár Farkas, M.D., New York, N. Y.
Henry Leon Feffer, M.D., Washington, D. C.

Leon J. Fox, M.D., St. Louis, Missouri
Elmer M. Franz, M.D., Denver, Colorado
Russell B. Graham, M.D., Dallas, Texas
Alfred A. Grebe, M.D., Fort Hood, Texas
Gerald S. Greene, M.D., Hartford, Connecticut
Vincent James Grillo, M.D., New Haven, Connecticut
Thomas Gucker, III, M.D., Warm Springs, Georgia
Isaac Gutman, M.D., Baltimore, Maryland
Stanley S. Haft, M.D., Los Angeles, California
Charles M. Hanisch, M.D., Brooklyn, N. Y.
Fred H. Hartshorn, M.D., Denver, Colorado
Alexander Hersh, M.D., New York, N. Y.
Robert P. Holt, M.D., San Antonio, Texas
Jim M. Hooks, M.D., Abilene, Texas
Walter Skellie Hunt, Jr., M.D., Raleigh, North Carolina
Robert Herrick Hutchinson, M.D., Tallahassee, Florida
Kenneth Borden Jacques, M.D., Los Angeles, California
Joseph M. Janes, M.D., Rochester, Minnesota
John Bennett Jarrott, M.D., Hutchinson, Kansas
Werner P. Jensen, M.D., Omaha, Nebraska
Rolf E. Johnson, M.D., Easton, Pennsylvania
Desmond Duane Kackley, M.D., Columbus, Ohio
Frank James Kelley, M.D., Detroit, Michigan
Otto C. Kestler, M.D., New York, N. Y.
John Jacob Killeffer, M.D., Chattanooga, Tennessee
Daniel M. Kingsley, M.D., Alexandria, Louisiana
Frederick J. Knocke, M.D., New York, N. Y.
Jacob Krause, M.D., Philadelphia, Pennsylvania
Loren J. Larsen, M.D., San Francisco, California
Edward A. Lebold, M.D., Salem, Oregon
Edward LeMoncheck, M.D., Los Angeles, California
Jack Levine, M.D., Brooklyn, N. Y.
Herman Lohman, M.D., Newark, New Jersey
Albert O. Loiselle, M.D., Dallas, Texas
Victor Mayer, M.D., New York, N. Y.
Howard A. Molter, M.D., Eugene, Oregon
William Thornton Mustard, M.D., Toronto, Ontario, Canada
Richard S. Neff, M.D., Fresno, California
Wendell J. Newcomb, M.D., Pensacola, Florida
William V. Newman, M.D., Little Rock, Arkansas
William I. Norton, M.D., Richmond, California
Richard T. Odell, M.D., St. Louis, Missouri
Gordon Blake O'Neil, M.D., Seattle, Washington
Alexander D. Papas, M.D., New York, N. Y.
Sterling G. Parker, M.D., Decatur, Illinois
Louis S. Peery, M.D., Ogden, Utah
Ralph C. Petersen, M.D., Glendale, California
Wendell C. Peterson, M.D., Albuquerque, New Mexico
Edgar L. Ralston, M.D., Philadelphia, Pennsylvania
Oscar S. Reeder, M.D., Washington, D. C.
Ralph Everett Reiner, M.D., Fort Sam Houston, Texas
Seymour Reissman, M.D., Brooklyn, New York
Jack Leahy Richardson, M.D., Tulsa, Oklahoma
Louis Paul Ripley, M.D., Roanoke, Virginia
Edgar A. Rogge, M.D., Seattle, Washington
Austin B. Rohrbaugh, Jr., M.D., Chevy Chase, Maryland
Robert Manser Rose, M.D., New Orleans, Louisiana
Robert Thorman Rosenfeld, M.D., Beverly Hills, California
Stuart Wells Russell, M.D., Hanover, New Hampshire
Carl M. Rylander, M.D., San Francisco, California
Edwin Richard Schottstaedt, M.D., San Francisco, California
Adolph Segal, M.D., San Francisco, California
A. Lewis Shure, M.D., New Haven, Connecticut
Aaron I. Simon, M.D., Fitchburg, Massachusetts

Samuel Berry Thompson, M.D., Little Rock, Arkansas
John F. Thurlow, M.D., Hays, Kansas
Marshall R. Urist, M.D., Los Angeles, California
John Alden Vann, M.D., Norfolk, Virginia
George Thomas Wallace, M.D., Spokane, Washington
Richard Kerr White, M.D., Allentown, Pennsylvania
Henry S. Wieder, Jr., M.D., Philadelphia, Pennsylvania
Howell Ernest Wiggins, M.D., Philadelphia, Pennsylvania
Leon L. Wiltse, M.D., Long Beach, California
Fred Ralph Zeiss, M.D., Chicago, Illinois

At the second Executive Session the following officers and committeemen were elected:
President: Francis M. McKeever, M.D., Los Angeles, California
President-Elect: Harold B. Boyd, M.D., Memphis, Tennessee
Vice-President: Herman F. Johnson, M.D., Omaha, Nebraska
Secretary: John R. Noreross, M. D., Chicago, Illinois
Treasurer: H. Relton McCarroll, M.D., St. Louis, Missouri
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The presidential medallion was presented to President Joseph S. Barr by Past-President Guy A. Caldwell. The gavel was presented to the new President, Dr. Francis M. McKeever, by the retiring President, Dr. Joseph S. Barr.

The Annual Dinner was held on Wednesday evening, at which time the Kappa Delta Award was made. Dr. Robert A. Robinson was the recipient of this award. Other awards were made as follows:
Scientific Exhibits
Class I: Research for Scientific Value:
1. A. R. Shands, Jr., M.D., Col. Knox Dunlap, Medical Corps, United States Army; Major L. C. Hollister, Jr., Medical Corps, United States Air Force; and Stuart Gaul, Jr., M.D., Wilmington, Delaware:
Technique for Determination of Torsion of Femur.
2. W. B. Looney, M.D., R. J. Hasterlik, M.D., A. M. Brues, M.D., L. D. Marinelli, M.A., W. P. Norris, Ph.D., and A. H. Stehney, Ph.D., Chicago, Illinois:
Clinical Investigation of Radium Toxicity.
3. Col. A. W. Spittler and Col. E. W. Hakala, Medical Corps, Walter Reed Army Hospital, Washington, D. C.:
Ideal Amputation Stumps.
Major Robert W. Parvin, and Major Coursen B. Conklin, Medical Corps, Walter Reed Army Hospital, Washington, D. C.:
Plastic Spints.
Lent C. Johnson, M.D., Gwilym S. Lodwick, M.D., and Col. William L. Thompson, Armed Forces Institute of Pathology, Registry of Orthopaedic Pathology, and Registry of Radiologic Pathology, Washington, D. C.:
Malignant Primary Tumors of the Bone.
Class II: Clinical Application:
1. Abel Kenin, M.D., and Melvin Jahss, M.D., New York, N. Y.:
Clinical and Pathological Follow-up of 208 Cases of Epiphysiolysis—One to Twenty-eight Year Follow-up.
2. C. E. Irwin, M.D., Warm Springs, Georgia, and Don L. Eyler, M.D., Nashville, Tennessee:
Poliomyelitis: Surgical Rehabilitation of the Thumb and Index Finger.
3. Lieut. Erle E. Peacock, Medical Corps, and Lieut. Col. Victor B. Vare, Medical Corps, Valley Forge Hospital, Phoenixville, Pennsylvania:
Inexpensive, Improved Dynamic Splints for Injured Hands.

Class III: Originality in Presentation of Exhibit:

1. Frederick Lee Liebolt, M.D., New York, N. Y. Injuries to the Menisci of the Knee Joint.
2. Herbert A. Lange, M.D., New York, N. Y., James Barnett, M.D., P. Dulligan, M.D., I. Brady, M.D., Herbert Fett, Jr., M.D., Thomas Gallagher, M.D., and Bertram Schneider, M.D., Brooklyn, New York:
   Is Your Congenital Hip Reduced?
3. H. F. Moseley, M.D., Montreal, Canada:
   Shoulder Lesions.

Gadget Exhibits

1. R. W. Coonrad, M.D., Durham, North Carolina, and C. E. Irwin, M.D., Warm Springs, Georgia:
   Flexible Shaft Drill Attachment for the Luck Bone Saw.
2. John R. Cobb, M.D., New York, N. Y.:
   Gouges and Mallet for Spine Fusions.

Audio-Visual Program

1. P. L. Rieth, Emory University, Georgia:
   Prop-Latch Spine Fusion Combined with Total Laminectomy.
2. C. O. Bechtol, Oakland, California:
   Gait Abnormalities Resulting from Variations in Joint Alignment.

The Twentieth Annual Convention will be held at the Palmer House, Chicago, January 24 to 29, 1953, under the presidency of Dr. Francis M. McKeever.

LETTER TO THE EDITOR

In the course of correspondence with John L. Young, Ph.D., Senior Fellow, Orthopaedic Appliance Fellowship, The Mellon Institute of Industrial Research, University of Pittsburgh, he wrote the following:

"The Orthopaedic Fellowship at Mellon Institute is sustained by the Sarah Mellon Scaife Foundation and one of the objects of the Fellowship is to develop new devices for orthopaedic physicians and surgeons. We, of course, assume that any equipment which we construct will be produced for sale by others, after the value of the new design has been adequately demonstrated.

"I think you should be informed that we have experienced difficulty on occasion in constructing equipment which is described in *The Journal of Bone and Joint Surgery* because a bill of materials and drawing were not included in the original article. We would be pleased to supply this information for *The Journal* as part of the Fellowship activities, if so requested. A number of bracemakers have reported the same difficulty and have also stated that they were unable to obtain complete information from the writers. It has been possible for us to supply drawings to bracemakers of our interpretation of many of these devices, as the bracemakers request our assistance when they find they cannot make the equipment shown in the photograph."

The writer also went on to say that Dr. Paul V. Hutchinson (see below) had offered to cooperate with them [the Fellowship] in this kind of assistance to *The Journal*, if requested. The writer states that Dr. Hutchinson was "employed as a construction engineer before he entered medical school and is much interested in *orthopaedic mechanics*".

The above correspondence developed subsequent to my writing to Dr. Hutchinson about an article which he had submitted to *The Journal* describing a forceps for use in the Bankart procedure. The Board of Associate Editors discussed this article one evening and felt that it should be published. Dr. Hutchinson had replied that so far none of the commercial houses had made the instrument, but that he had turned over the idea to Dr. Young, asking him to construct one of the instruments and send it to me. It now develops that Dr. Hutchinson supplied Dr. Young with a pair of uterine forceps which he then had modified as per the design submitted to *The Journal* by Dr. Hutchinson.

In summary, it seemed to me that the services of the Institute, notably the Orthopaedic Appliance Fellowship men, might be of definite value to *The Journal* or to a reader thereof, in furnishing specific drawings, data, and so forth, upon which, in turn, the instrument in question could be constructed.

G. Edmund Haggart, M.D.
605 Commonwealth Avenue
Boston 15, Massachusetts

January 14, 1952

Wanted

The Editorial Office of *The Journal* is constantly having calls for back issues of *The Journal* and desires to know where copies of the following issues may be obtained when needed:

THE AMERICAN JOURNAL OF ORTHOPEDIC SURGERY

1903–1904: Vol. I, Nos. 1, 2, 3, and 4; August, November 1903; February, May 1904.
1904–1905: Vol. II, Nos. 1, 2, 3, and 4; August, October 1904; January, April 1905.
1905–1906: Vol. III, Nos. 1, 3, and 4; July 1905; January, April 1906.
1906–1907: Vol. IV, Nos. 1, 2, 3, and 4; July, October 1906; January, April 1907.
1907–1908: Vol. V, Nos. 1, 2, 3, and 4; July, October 1907; January, April 1908.
1908–1909: Vol. VI, Nos. 1, 2, 3, and 4; August, November 1908; February, May 1909.
1909–1910: Vol. VII, Nos. 1, 2, 3, and 4; August, November 1909; February, May 1910.
1910–1911: Vol. VIII, Nos. 1, 2, 3, and 4; August, November 1910; February, May 1911.
1911–1912: Vol. IX, Nos. 1, 2, 3, and 4; August, November 1911; February, May 1912.
1912–1913: Vol. X, Nos. 1, 2, 3, and 4; August, November 1912; February, May 1913.
1913–1914: Vol. XI, Nos. 1, 2, 3, and 4; July, October 1913; January, April 1914.
1914–1915: Vol. XII, Nos. 1, 2, 3, and 4; July, October 1914; January, April 1915.
1915: Vol. XIII, Nos. 1 and 2; July, October.
1916: Vol. XIV, All twelve issues.
1917: Vol. XV, Nos. 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; January. February, March, April, May, June, July, August, September, and October.
1918: Vol. XVI, Nos. 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, and 12; January, February, March, April, June, July, August, September, October, November, and December.

THE JOURNAL OF ORTHOPAEDIC SURGERY

1919: Vol. I (Old Series Vol. XVII), Nos. 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, and 12; January, February, March, April, May, June, July, September, October, November, and December.
1920: Vol. II (Old Series Vol. XVIII), Nos. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12; February, March, April, May, June, July, August, September, October, November, December.
1921: Vol. III (Old Series Vol. XIX), Nos. 1, 2, 3, 4, 6, 9, 10, 11, and 12; January, February, March, April, June, September, October, November, and December.

THE JOURNAL OF BONE AND JOINT SURGERY

1922: Vol. IV (Old Series Vol. XX), Nos. 1 and 2; January and April.
1923: Vol. V (Old Series Vol. XXI), Nos. 1, 2, 3, and 4; January, April, July, and October.
1924: Vol. VI (Old Series Vol. XXII), Nos. 1, 2, 3, and 4; January, April, July, and October.
1925: Vol. VII (Old Series Vol. XXIII), No. 1; January.
1926: Vol. VIII (Old Series Vol. XXIV), Nos. 1, 2, 3, and 4; January, April, July, and October.
1927: Vol. IX (Old Series Vol. XXV), Nos. 1, 2, 3, and 4; January, April, July, and October.
1928: Vol. X (Old Series Vol. XXVI), Nos. 1, 2, and 3; January, April, and July.
1929: Vol. XI (Old Series Vol. XXVII), Nos. 1, 2, and 4; January, April, and October.
1930: Vol. XII (Old Series Vol. XXVIII), No. 1; January.
1931: Vol. XIII (Old Series Vol. XXIX), No. 1; January.
1932: Vol. XIV (Old Series Vol. XXX), No. 4; October.
1934: Vol. XVI (Old Series Vol. XXXII), No. 4; October.
1935: Vol. XVII (Old Series Vol. XXXIII), Nos. 1, 2, and 4; January, April, and October.
1937: Vol. XIX (Old Series Vol. XXXV), Nos. 1, 3, and 4; January, July, and October.
1938: Vol. XX (Old Series Vol. XXXVI), Nos. 1, 2, 3, and 4; January, April, July, and October.
1939: Vol. XXI (Old Series Vol. XXXVII), Nos. 1, 2, 3, and 4; January, April, July, and October.
1940: Vol. XXII (Old Series Vol. XXXVIII), No. 1; January.
1941: Vol. XXIII (Old Series Vol. XXXIX), No. 1; January.
1944: Vol. XXVI (Old Series Vol. XLII), Nos. 1, 2, 3, and 4; January, April, July, and October.
1947: Vol. 29 (Old Series Vol. 45), Nos. 1, 2, and 3; January, April, and July.
1948: Vol. 30-A, No. 1; January.

Any reader having copies of the above, which he is willing to dispose of, is requested to correspond with the Editor.

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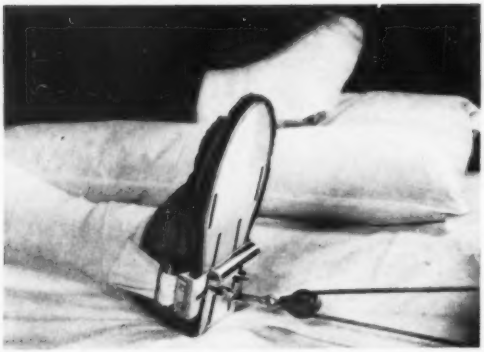

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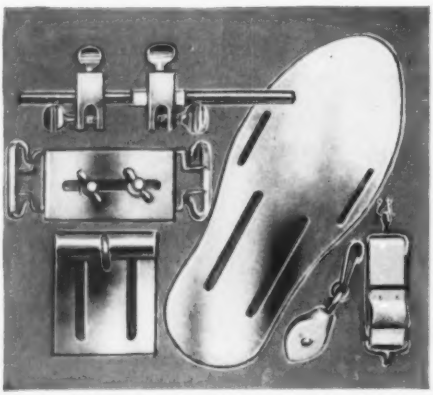

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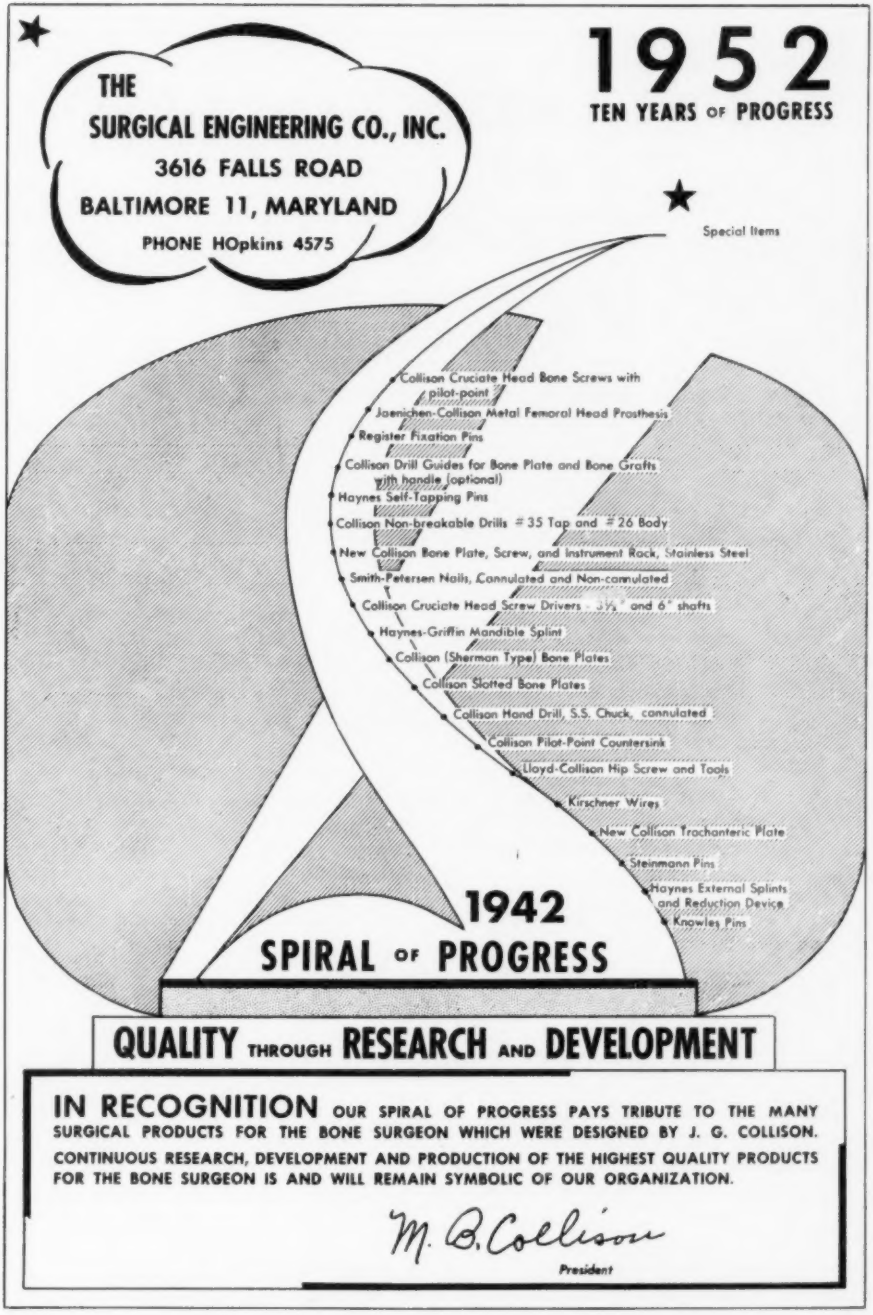
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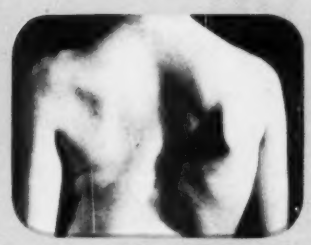
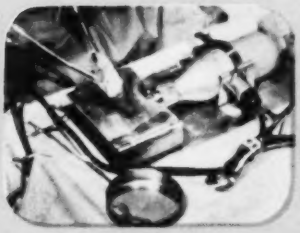


Patient with idiopathic scoliosis.

Surgeon beginning the operation.

Spine prepared for fusion.



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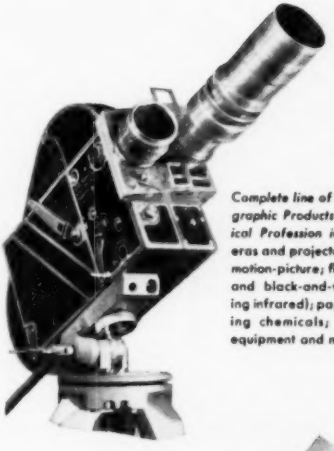

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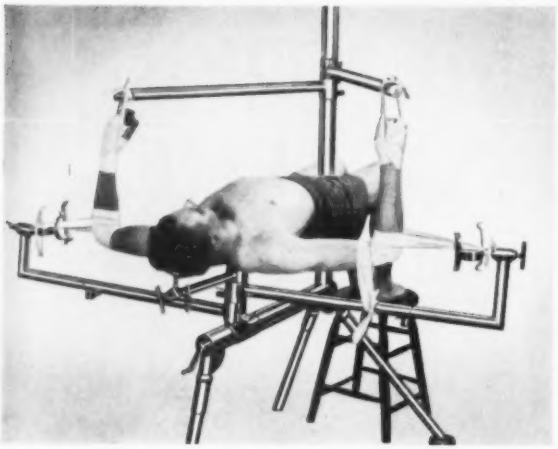

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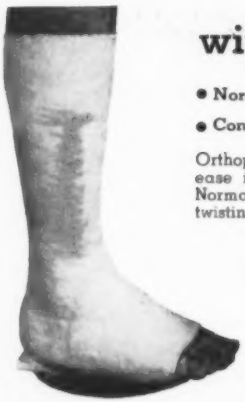

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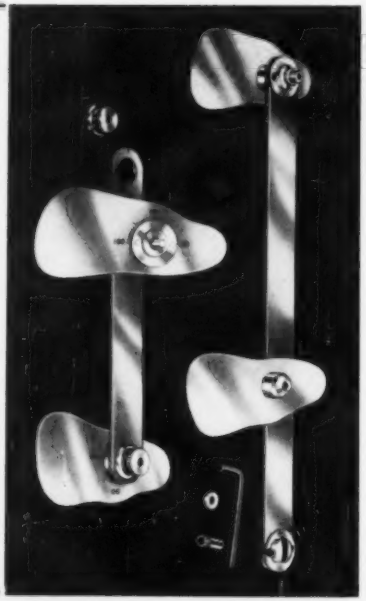

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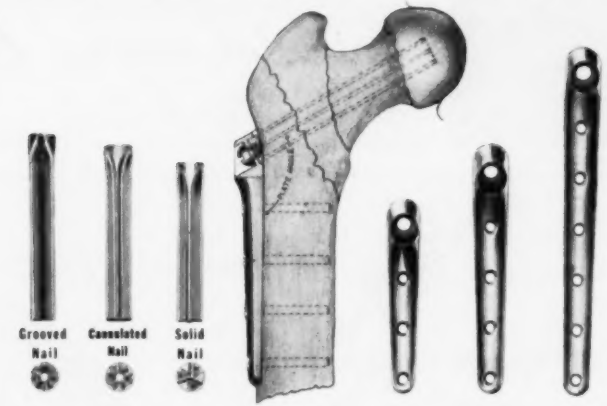

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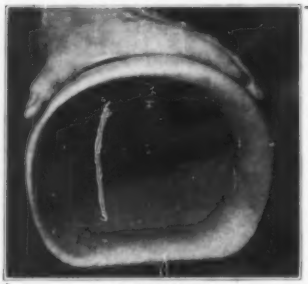

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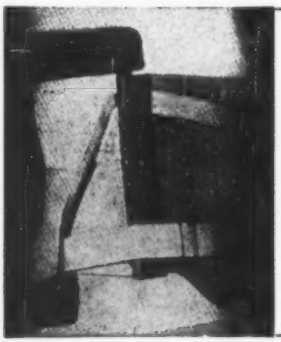

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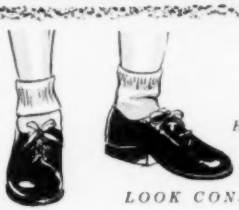

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